L3 ANSWER 2 OF 2 MEDLINE
ACCESSION NUMBER: 85116068 MEDLINE
DOCUMENT NUMBER: 85116068 PubMed ID: 6523394
TITLE: [Artificial synovial fluid for the intra-articular treatment of rheumatoid **arthritis** and osteoarthritis (chemical synthesis and clinico-experimental and biomechanical data)]. Iskusstvennaia sinovial'naia zhidkost' dlia vnutrisustavnogo lecheniia revmatoidnogo artrita i osteoartroza (razrabotka, kliniko-eksperimental'noe i biomekhanicheskoe obosnovanie).
AUTHOR: Vadilenkaitis V V; Matulis A A
SOURCE: TERAPEVTICHESKII ARKHIV, (1984) 56 (11) 73-7.
Journal code: 2984818R. ISSN: 0040-3660.
PUB. COUNTRY: USSR
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: Russian
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198503
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19980206
Entered Medline: 19850314

AB Based on the clinical, experimental and biomechanical studies the authors suggest intraarticular treatment of rheumatoid **arthritis** (RA) and deforming osteoarthrosis (DOA) by means of artificial synovial fluid (ASF) developed with the use of polymers and biopolymers. Rheological studies performed with the use of a Rheotest-2 apparatus and ultrasonic interferometry of the samples of normal, RA, DOA synovial fluid and ASF demonstrated that medium-molecular-weight **polyvinylpyrrolidone** (PVP) and PVP hyaluronate appeared the most similar to natural synovial fluid, PVP-hyaluronate, PVP and its complexes with other drugs (cyclophosphamide, hydrocortisone, arteparone) were applied intraarticularly to the treatment of 520 patients with RA and DOA. The group of patients who received kenalog or placebo intraarticularly served as control. Over 3000 intraarticular administrations of ASF and its complexes were made altogether. No side effects were observed. In the articular medium, PVP displayed lubrication, anti-inflammatory, prolonging, anticommissural and other effects. Attention is drawn to the immunoregulatory action of PVP. The treatment with artificial articular lubricants promoted the improvement of the function of the joints and positive time-course of some clinical, laboratory, biochemical and immunological characteristics.

L6 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:274742 CAPLUS
DOCUMENT NUMBER: 138:292429
TITLE: W/O/W composite emulsions containing specified **water**-soluble film-forming polymers and silicone oils
INVENTOR(S): Nakagawa, Taiji
PATENT ASSIGNEE(S): Kanebo, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003104861	A2	20030409	JP 2001-299705	20010928

PRIORITY APPLN. INFO.: JP 2001-299705 20010928

AB The invention relates to a W/O/W composite emulsion having excellent storage stability and use feel, suitable for use in a pharmaceutical or cosmetic compn., wherein the emulsion is characterized by contg. (1) gum arabic, alginic acid, carrageenan, agar, guar gum, quince seed, tamarind gum, dextrin, dextran, starch, locust bean gum, karaya gum, gum tragacanth, pectin, quince, chitosan, xanthan gum, gellan gum, **hyaluronic acid**, pullulan, Me cellulose, Et cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl Me cellulose, CM-cellulose, cationized cellulose, polyacrylic acid amide, polyvinyl alc., and/or polyvinyl pyrrolidone, and (2) a silicone oil, and wherein the emulsion has a **viscosity** at 30.degree. of 3000-15000 mPa.cntdot.s. The emulsion may further contain a silicone surfactant.

L6 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:76525 CAPLUS
DOCUMENT NUMBER: 138:142458
TITLE: Biodegradable injectable implants and related methods of manufacture and use
INVENTOR(S): Caseres, Crisofo Peralta; D'Lagarde, Daniel Leon
PATENT ASSIGNEE(S): Medgraft Microtech, Inc., Mex.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007782	A2	20030130	WO 2002-US20802	20020628

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: MX 2001-6732 A 20010629
US 2001-2283 A 20011205

AB This invention is directed to the field of medical implants, and more specifically to biodegradable injectable implants and their methods of manuf. and use. The injectable implants disclosed herein comprise

glycolic acid and bio-compatible/bio-absorbable polymeric particles contg. a polymer of lactic acid. The particles are small enough to be injected through a needle but large enough to avoid engulfment by macrophages. The injectables of this invention may be in a pre-activated solid form or an activated form (e.g., injectable suspension or emulsion). For example, a lyophilized compn. was prepd. contg. glycolic acid 0.07 mg, poly(lactic acid) spheres 200.0 mg, hydroxypropyl Me cellulose 118.33 mg, D-mannitol 170.0 mg, pH stabilizer (phosphate buffer) 0.50 mg, and surfactant (Tween 80) 1.20 mg. The compn. was activated extemporaneously with 5.5 mL **water** to obtain an injectable prepn.

L6 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107048 CAPLUS
DOCUMENT NUMBER: 136:156435
TITLE: Pharmaceutical compositions for the treatment of inflammatory and ulcerative conditions of moist epithelial surfaces such as mucositis, stomatitis and Behcet's syndrome
INVENTOR(S): Mastrodonato, Marco
PATENT ASSIGNEE(S): Sinclair Pharma S.r.l., Italy
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009637	A2	20020207	WO 2001-EP8303	20010718
WO 2002009637	A3	20021205		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
AU 2002012113	A5	20020213	AU 2002-12113	20010718

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
WO 2001-EP8303 W 20010718

AB Pharmaceutical compns. comprising as active ingredients EDs of **hyaluronic acid**, glycyrrhetinic acid and **polyvinylpyrrolidone**, for the treatment of painful, inflammatory. and ulcerative conditions of moist epithelial surfaces such as mucositis and Behcet's syndrome. Thus, a formulation contained sodium hyaluronate 0.1, glycyrrhetinic acid 0.06, PVP 9.0, maltodextrin 6.00, propylene glycol 2.94, potassium sorbate 0.3, sodium benzoate 0.3, hydroxyethyl cellulose 1.5, hydrogenated castor oil PEG-40 0.27, disodium EDTA 0.1, benzalkonium chloride 0.5, perfume (Glycyrrhiza ext.) 0.16, sodium saccharin 0.1, and **water** 78.44%.

L6 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:861512 CAPLUS
DOCUMENT NUMBER: 134:32938
TITLE: Keratinocyte Growth Factor-2 formulations
INVENTOR(S): Gentz, Reiner L.; Chopra, Arvind; Kaushal, Parveen; Spitznagel, Thomas; Unsworth, Edward; Khan, Fazal
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2

L6 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:116749 CAPLUS
DOCUMENT NUMBER: 132:156550
TITLE: High **viscosity** make-up composition containing an aqueous polymer dispersion
INVENTOR(S): Bara, Isabelle; Jager-Lezer, Nathalie
PATENT ASSIGNEE(S): L'Oreal, Fr.
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 979642	A1	20000216	EP 1999-401776	19990715
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
FR 2782267	A1	20000218	FR 1998-10332	19980812
FR 2782267	B1	20010511		
BR 9903433	A	20000926	BR 1999-3433	19990802
JP 2000063240	A2	20000229	JP 1999-228059	19990811

PRIORITY APPLN. INFO.: FR 1998-10332 A 19980812

AB A cosmetic compn. contains an aq. polymer dispersion, and a thickening agent q.s. to give a **viscosity** of .gtoreq.4.5 and .ltoreq.1000 Pa.s at 25.degree.. A cosmetic compn. contained Sancure 861 (an aq. dispersion of polyurethane) 75, Serad FX1100 (a polyurethane) 3, pigment 5, ethanol 7, preservatives q.s., and **water** q.s. 100%.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072872	A1	20001207	WO 2000-US15186	20000602
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1196187	A1	20020417	EP 2000-941186	20000602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003500456	T2	20030107	JP 2000-620980	20000602

PRIORITY APPLN. INFO.: US 1999-137448P P 19990602
US 1999-160913P P 19991022
WO 2000-US15186 W 20000602

AB The invention is directed to liq. and lyophilized forms of Keratinocyte Growth Factor-2 (KGF-2) and derivs. thereof. This invention further relates to the formulations of KGF-2 for therapeutic use, for example, to promote or accelerate wound healing.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:116749 CAPLUS
DOCUMENT NUMBER: 132:156550
TITLE: High **viscosity** make-up composition containing an aqueous polymer dispersion
INVENTOR(S): Bara, Isabelle; Jager-Lezer, Nathalie
PATENT ASSIGNEE(S): L'Oreal, Fr.
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 979642	A1	20000216	EP 1999-401776	19990715
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
FR 2782267	A1	20000218	FR 1998-10332	19980812
FR 2782267	B1	20010511		
BR 9903433	A	20000926	BR 1999-3433	19990802
JP 2000063240	A2	20000229	JP 1999-228059	19990811

PRIORITY APPLN. INFO.: FR 1998-10332 A 19980812

AB A cosmetic compn. contains an aq. polymer dispersion, and a thickening agent q.s. to give a **viscosity** of .gtoreq.4.5 and .ltoreq.1000 Pa.s at 25.degree.. A cosmetic compn. contained Sancure 861 (an aq. dispersion of polyurethane) 75, Serad FX1100 (a polyurethane) 3, pigment 5, ethanol 7, preservatives q.s., and **water** q.s. 100%.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1989:639516 CAPLUS
DOCUMENT NUMBER: 111:239516
TITLE: Stable lyophilized formulations containing growth factors
INVENTOR(S): Finkenaur, Amy L.; Cohen, Jonathan M.
PATENT ASSIGNEE(S): Ethicon, Inc., USA
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 308238	A1	19890322	EP 1988-308573	19880916
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE				
AU 8822236	A1	19890323	AU 1988-22236	19880914
DK 8805167	A	19890319	DK 1988-5167	19880916
JP 01121223	A2	19890512	JP 1988-232101	19880916
ZA 8806943	A	19900530	ZA 1988-6943	19880916

PRIORITY APPLN. INFO.: US 1987-98817 19870918
AB A stable lyophilized compn. comprises a polypeptide growth factor having human mitogenic or angiogenic activity and a **water**-sol. or **water**-swellable polymer capable of imparting **viscosity** to a reconstituted soln. of the compn. A compn. contg. EGF 50 .mu.g and mannitol 50 mg was lyophilized by freezing at -55.degree. at 1 atm for 4 h, -25.degree. at 1 atm for 4 h, and -55.degree. for 0.5 h at full vacuum. The lyophilized cake was stable for at least 209 days at 37.degree..

L6 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:540911 CAPLUS
DOCUMENT NUMBER: 107:140911
TITLE: Cosmetics containing acylated lysines and polymers
INVENTOR(S): Mori, Kunihiko; Kawai, Mitsuo
PATENT ASSIGNEE(S): Pola Chemical Industries, Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62126107	A2	19870608	JP 1985-266779	19851127

PRIORITY APPLN. INFO.: JP 1985-266779 19851127
AB A film-forming cosmetic contains (1) N-acylated lysine 0.01-5.0, (2) a **water**-sol. polymer 0.05-20.0, and (3) H2O or an EtOH soln. 50-99% by wt. (**viscosity**, .gtoreq.3000 cP). The acylated lysines are R1NH(CH2)4CH(NHR2)CO2H (R1 and R2 = H or C8-22 acyl and at least one of these Rs is acyl) such as N-(2-ethylhexyl)lysine. The polymer is poly(acrylic acid), poly(methacrylic acid), **polyvinylpyrrolidone**, or their derivs. This cosmetic applied to the skin is not washed off by perspiration or body fluids excreted from the skin. Thus, an eye liner was prepd. consisting of microcryst. wax 2, beeswax 8, fatty acid sorbitan esters 2, polyoxyethylene sorbitan fatty acid ester 2, Et cellulose 2, Arabic gum 1, a dye 10, H2O 72.9, and N-lauroyllysine 0.1 part by wt.

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(FILE 'HOME' ENTERED AT 16:52:13 ON 08 MAY 2003)

FILE 'CAPLUS' ENTERED AT 16:52:27 ON 08 MAY 2003

L1	0	S	HYALURONIC ADJ ACID
L2	11020	S	HYALURONIC ACID
L3	92	S	L2 AND POLYVINYLPYRROLIDONE
L4	42	S	L3 AND WATER
L5	17	S	L3 AND AQUEOUS
L6	7	S	L4 AND VISCOSITY
L7	0	S	L6 AND CENTIPOISE

L9 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:928236 CAPLUS
DOCUMENT NUMBER: 138:315
TITLE: Compositions and methods using **hyaluronic acid** and **polyvinylpyrrolidone** for the treatment or prevention of inflammation
INVENTOR(S): Mastrodonato, Marco; Braguti, Gianluca
PATENT ASSIGNEE(S): Pennie + Edmonds Llp, Italy
SOURCE: U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 80,624.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002183278	A1	20021205	US 2002-80736	20020222
IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
US 2002173485	A1	20021121	US 2002-80624	20020221

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
US 2002-80624 A2 20020221

AB The present invention relates to compds. contg. as active ingredients **hyaluronic acid** and **polyvinylpyrrolidone**, for the treatment of inflammatory, ulcerative and painful conditions of moist epithelial surfaces such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, and Behcet's syndrome.

L9 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:171621 CAPLUS
DOCUMENT NUMBER: 136:205519
TITLE: Polymer compositions for tissue augmentation
INVENTOR(S): Dyer, Wallace K.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002017816	A1	20020307	WO 2001-US27142	20010830
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001088585	A5	20020313	AU 2001-88585	20010830

PRIORITY APPLN. INFO.: US 2000-229085P P 20000830
US 2000-229989P P 20000905
US 2000-241636P P 20001019
WO 2001-US27142 W 20010830

AB The present invention comprises compns. comprising a combination of materials, comprising preferably a solid polymer particle phase and a **gel** phase, and also comprises single phase compns. More particularly, preferred embodiments comprise a solid polymer particle

phase made of materials comprising Gore-Tex (micronized e-PTFE), PDS II (polydioxanone, a monofilament), Nurolon (a long chain aliph. polymer Nylon 6 or Nylon 6,6) Ethison (a long chain aliph. polymer Nylon 6 and Nylon 6,6), Prolene (polypropylene, isotactic cryst. stereoisomer of polypropylene, a synthetic linear polyolefin.), Vicryl (copolymer made from 90 glycolide and 10 L-lactide), silk, Monacryl (poly .epsilon.-caprolactone.), polylactide, polyglycolide, poly lactide-co-glycolide, and Biopol (polyhydroxyvalerate), Medpor (biocompatible (micronized) polyethylene), Bioglass (bioactive glass particulate), Novabone and Nova Bone-CM, and the **gel** phase comprises **polyvinylpyrrolidone** (PVP). Preferred single phase compns. comprise PVP. Methods of the present invention comprising injection of such compns. for tissue augmentation.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:319774 CAPLUS
DOCUMENT NUMBER: 134:331686
TITLE: Medical use of tissue bonding materials
INVENTOR(S): Edwardson, Peter; Velada, Jose
PATENT ASSIGNEE(S): Tissuemed Ltd., UK
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001030410	A1	20010503	WO 2000-GB4154	20001027
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2002034304	A1	20020502	WO 2001-GB4682	20011022
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001095765	A5	20020506	AU 2001-95765	20011022

PRIORITY APPLN. INFO.:

GB 1999-25379	A	19991028
GB 2000-25882	A	20001023
WO 2000-GB4154	W	20001027
GB 2001-10881	A	20010503
GB 2001-19193	A	20010807
GB 2001-19196	A	20010807
WO 2001-GB4682	W	20011022

AB There is described the use of tissue bonding materials, i.e. materials by which body tissues can be caused to adhere together, to prevent the undesired formation of connective tissue between adjacent tissues following surgery (post-surgical adhesion). The tissue bonding material is preferably a protein or the like, most preferably albumin, and is

formulated as either a liq. or **gel**, or as a flexible sheet which can be applied to the tissues and caused to cure. For example, a viscous liq. formulation was prepd. contg. (by wt.) porcine albumin 41%, methylene blue 0.24%, glycerol 2%, and **water** up to 100%. The resulting viscous soln. can be applied to exposed tissues by spraying, and cured by the application of laser or polychromatic light. On completion of curing the color changed from blue to colorless.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:240923 CAPLUS
DOCUMENT NUMBER: 132:270089
TITLE: Synergistic antimicrobial, dermatological and ophthalmic preparations containing chlorite and hydrogen peroxide
INVENTOR(S): Karagoezian, Hampar L.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000019981	A1	20000413	WO 1999-US23291	19991006
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9964169	A1	20000426	AU 1999-64169	19991006
EP 1119347	A1	20010801	EP 1999-951810	19991006
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 6488965	B1	20021203	US 2000-722919	20001127

PRIORITY APPLN. INFO.: US 1998-169620 A 19981008
WO 1999-US23291 W 19991006

AB Disclosed are antimicrobial/pharmaceutical prepns. (e.g., solns., **gels**, ointments, creams, sustained release prepns., etc.) which include chlorite (e.g., a metal salt of a chlorite) in combination with a peroxy compd. (e.g., hydrogen peroxide), and methods for using such prepns. for disinfection of articles or surfaces (e.g., contact lenses, counter tops, etc.), antisepsis of skin or other body parts, prevention or deterrence of scar formation and/or treatment and prophylaxis of dermal (i.e., skin or mucous membrane) disorders (e.g., wounds, burns, infections, cold sores, ulcerations, psoriasis, acne, or other scar-forming lesions). A **gel** contg. Na chlorite 0.06, H2O2 0.01, hydroxypropyl Me cellulose 2, boric acid 0.15, HCl/NaOH q.s. to pH 7.4, and purified **water** q.s. to 100 % was formulated and applied on the affected arms to treat psoriasis plaques.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:467217 CAPLUS
DOCUMENT NUMBER: 125:137244
TITLE: **Gels** for encapsulation of biological materials
INVENTOR(S): Hubbell, Jeffrey A.; Pathak, Chandrashekhar P.;

Sawhney, Amarpreet S.; Desai, Neil P.; Hossainy, Syed F. A.
PATENT ASSIGNEE(S): University of Texas System, USA
SOURCE: U.S., 34 pp., Cont.-in-part of U.S. Ser. No. 870, 540.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5529914	A	19960625	US 1992-958870	19921007
US 5232984	A	19930803	US 1991-740632	19910805
US 5380536	A	19950110	US 1991-740703	19910805
WO 9316687	A1	19930902	WO 1993-US1776	19930301
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9337809	A1	19930913	AU 1993-37809	19930301
AU 683209	B2	19971106		
EP 627912	A1	19941214	EP 1993-907078	19930301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07506961	T2	19950803	JP 1993-515100	19930301
JP 3011767	B2	20000221		
US 5573934	A	19961112	US 1993-24657	19930301
BR 9306041	A	19971118	BR 1993-6041	19930301
CA 2117584	C	19980922	CA 1993-2117584	19930301
US 5858746	A	19990112	US 1995-377911	19950125
US 5834274	A	19981110	US 1995-467693	19950606
US 5843743	A	19981201	US 1995-467815	19950606
US 5801033	A	19980901	US 1995-480678	19950607
US 6258870	B1	20010710	US 1997-783387	19970113
US 6231892	B1	20010515	US 1997-969910	19971113
US 6465001	B1	20021015	US 1998-33871	19980303
US 2002058318	A1	20020516	US 2001-811901	20010319

PRIORITY APPLN. INFO.:

US 1990-598880	B2	19901015
US 1991-740632	A3	19910805
US 1991-740703	A2	19910805
US 1992-843485	B2	19920228
US 1992-870540	A2	19920420
US 1992-958870	A	19921007
US 1993-24657	A1	19930301
WO 1993-US1776	A	19930301
US 1994-232054	A3	19940428
US 1994-336393	A3	19941110
US 1995-467693	A1	19950606
US 1995-475175	A2	19950607
US 1995-484160	B3	19950607
US 1997-783387	A1	19970113

AB This invention provides novel methods for the formation of biocompatible membranes around biol. materials using photopolymn. of **water**-sol. mols. The membranes can be used as a covering to encapsulate biol. materials or biomedical devices, as a ''glue'' to cause >1 biol. substance to adhere together, or as carriers for biol. active species. Several methods for forming these membranes are provided. Each of these methods utilizes a polymn. system contg. **water**-sol. macromers, species which are at once polymers and macromols. capable of further polymn. The macromers are polymd. by using a photoinitiator (such as a dye), optionally a cocatalyst, optionally an accelerator, and radiation in the form of visible or long-wavelength UV light. The reaction occurs either by suspension polymn. or by interfacial polymn. The polymer membrane can be formed directly on the surface of the biol. material, or it can be formed on material which is already encapsulated.

L9 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:610747 CAPLUS
DOCUMENT NUMBER: 119:210747
TITLE: **Gels** for encapsulation of biological materials.
INVENTOR(S): Hubbell, Jeffrey A.; Pathak, Chandrashekhar P.; Sawhney, Amarpreet S.; Desai, Neil P.; Hill, Jennifer L.; Hossainy, Syed F. A.
PATENT ASSIGNEE(S): University of Texas System, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9316687	A1	19930902	WO 1993-US1776	19930301
W: AU, BB, BG, BR, CA, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5529914	A	19960625	US 1992-958870	19921007
AU 9337809	A1	19930913	AU 1993-37809	19930301
AU 683209	B2	19971106		
EP 627912	A1	19941214	EP 1993-907078	19930301
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 07506961	T2	19950803	JP 1993-515100	19930301
JP 3011767	B2	20000221		
BR 9306041	A	19971118	BR 1993-6041	19930301

PRIORITY APPLN. INFO.:
US 1992-843485 A 19920228
US 1992-870540 A 19920420
US 1992-958870 A 19921007
US 1990-598880 B2 19901015
US 1991-740632 A3 19910805
US 1991-740703 A2 19910805
WO 1993-US1776 A 19930301

AB **Water**-sol. macromers are modified by addn. of free radical-polymerizable groups, such as those contg. a CC double or triple bond, which can be polymd. under mild conditions to encapsulate tissues, cells, or biol. active materials. The polymeric materials are particularly useful as tissue adhesives, coatings for tissue lumens, including blood vessels, coatings for cells, such as islets of Langerhans, coatings, plugs, supports or substrates for contact with biol. materials, and as drug delivery system. Human Langerhans islets were encapsulated in a PEG tetraacrylate macromer **gel** by interfacial polymn., using ethyl eosin initiator.

L9 ANSWER 7 OF 7 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:617804 CAPLUS
DOCUMENT NUMBER: 113:217804
TITLE: Wrinkle-masking composition containing film-forming polymers
INVENTOR(S): Kawan, Antoine
PATENT ASSIGNEE(S): Gillette Co., USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9004383	A1	19900503	WO 1989-US4624	19891016
W: JP				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
US 4965071	A	19901023	US 1988-259713	19881019
CA 2000866	AA	19900419	CA 1989-2000866	19891017

PRIORITY APPLN. INFO.: US 1988-259713 19881019

AB A wrinkle-masking compn. temporarily eliminates fine line wrinkles and blemishes of the skin by filling, covering, or masking them. The compn. includes a film-forming polymer, a plasticizer for the polymeric matrix, a biopolymeric modifier and a filler including aluminosilicate. Optionally, the compn. includes cosmetic additives, e.g., pigments, rheol. control agents, binders and preservatives. The compn. is easy to apply, rapidly dries to a satisfactory texture, and is resistant to skin secretion which enhances the long wearing capabilities of the compn. The dried compn. effectively covers the fine line wrinkles of the face. Thus, a wrinkle-masking **gel** consisted of Flexan 130 (30%) 2.43, CMC-7MP 2.43, PEG 4.05, glycerin 6.49, hexylene glycol 1.22, **hyaluronic acid** (1%) 0.81, Pancogene-S (0.3%) 4.05, Avicel RC-591 1.62, Valfor Z81-352 2.03, Amihope-LL 0.08, Carbopol 941 0.08, Kathon CG 0.65 and distd. **water** 74.06 g.

L14 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:274742 CAPLUS
DOCUMENT NUMBER: 138:292429
TITLE: W/O/W composite emulsions containing specified water-soluble film-forming polymers and silicone oils
INVENTOR(S): Nakagawa, Taiji
PATENT ASSIGNEE(S): Kanebo, Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003104861	A2	20030409	JP 2001-299705	20010928

PRIORITY APPLN. INFO.: JP 2001-299705 20010928

AB The invention relates to a W/O/W composite emulsion having excellent storage stability and use feel, suitable for use in a pharmaceutical or cosmetic compn., wherein the emulsion is characterized by contg. (1) gum arabic, alginic acid, carrageenan, agar, guar gum, quince seed, tamarind gum, dextrin, dextran, starch, locust bean gum, karaya gum, gum tragacanth, pectin, quince, chitosan, xanthan gum, gellan gum, **hyaluronic acid**, pullulan, Me cellulose, Et cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl Me cellulose, CM-cellulose, cationized cellulose, polyacrylic acid amide, polyvinyl alc., and/or polyvinyl pyrrolidone, and (2) a silicone oil, and wherein the emulsion has a **viscosity** at 30.degree. of 3000-15000 mPa.cntdot.s. The emulsion may further contain a silicone surfactant.

L14 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:76525 CAPLUS
DOCUMENT NUMBER: 138:142458
TITLE: Biodegradable injectable implants and related methods of manufacture and use
INVENTOR(S): Caseres, Crisofo Peralta; D'Lagarde, Daniel Leon
PATENT ASSIGNEE(S): Medgraft Microtech, Inc., Mex.
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003007782	A2	20030130	WO 2002-US20802	20020628

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: MX 2001-6732 A 20010629
US 2001-2283 A 20011205

AB This invention is directed to the field of medical implants, and more specifically to biodegradable injectable implants and their methods of manuf. and use. The injectable implants disclosed herein comprise glycolic acid and bio-compatible/bio-absorbable polymeric particles contg.

a polymer of lactic acid. The particles are small enough to be injected through a needle but large enough to avoid engulfment by macrophages. The injectables of this invention may be in a pre-activated solid form or an activated form (e.g., injectable suspension or emulsion). For example, a lyophilized compn. was prepd. contg. glycolic acid 0.07 mg, poly(lactic acid) spheres 200.0 mg, hydroxypropyl Me cellulose 118.33 mg, D-mannitol 170.0 mg, pH stabilizer (phosphate buffer) 0.50 mg, and surfactant (Tween 80) 1.20 mg. The compn. was activated extemporaneously with 5.5 mL water to obtain an injectable prepn.

L14 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107048 CAPLUS
DOCUMENT NUMBER: 136:156435
TITLE: Pharmaceutical compositions for the treatment of inflammatory and ulcerative conditions of moist epithelial surfaces such as mucositis, stomatitis and Behcet's syndrome
INVENTOR(S): Mastrodonato, Marco
PATENT ASSIGNEE(S): Sinclair Pharma S.r.l., Italy
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009637	A2	20020207	WO 2001-EP8303	20010718
WO 2002009637	A3	20021205		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
AU 2002012113	A5	20020213	AU 2002-12113	20010718

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
WO 2001-EP8303 W 20010718

AB Pharmaceutical compns. comprising as active ingredients EDs of **hyaluronic acid**, glycyrrhetinic acid and **polyvinylpyrrolidone**, for the treatment of painful, inflammatory and ulcerative conditions of moist epithelial surfaces such as mucositis and Behcet's syndrome. Thus, a formulation contained sodium hyaluronate 0.1, glycyrrhetinic acid 0.06, PVP 9.0, maltodextrin 6.00, propylene glycol 2.94, potassium sorbate 0.3, sodium benzoate 0.3, hydroxyethyl cellulose 1.5, hydrogenated castor oil PEG-40 0.27, disodium EDTA 0.1, benzalkonium chloride 0.5, perfume (Glycyrrhiza ext.) 0.16, sodium saccharin 0.1, and water 78.44%.

L14 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:214825 CAPLUS
DOCUMENT NUMBER: 134:256921
TITLE: Dental porcelain paste using **viscosity**-controlled binder solutions
INVENTOR(S): Sato, Maohiro; Ikushima, Keisuke
PATENT ASSIGNEE(S): Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent

L14 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:214825 CAPLUS
DOCUMENT NUMBER: 134:256921
TITLE: Dental porcelain paste using **viscosity** -controlled binder solutions
INVENTOR(S): Sato, Maohiro; Ikushima, Keisuke
PATENT ASSIGNEE(S): Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 10 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001079019	A2	20010327	JP 1999-261427	19990916
GB 2355266	A1	20010418	GB 2000-22340	20000912
US 6444597	B1	20020903	US 2000-662140	20000914
DE 10045663	A1	20010523	DE 2000-10045663	20000915

PRIORITY APPLN. INFO.: JP 1999-261427 A 19990916

AB The paste, which are easily handled by unskilled dental technicians and used for making dental porcelain such as crowns, comprises 7-45 wt. parts binder and porcelain powder balance, and the binder contains (a) .gtoreq.1 org. solvents selected from di- or trihydric alcs., hydroxy-contg. ethers, and hydroxy(meth)acrylates and/or H2O and (b) synthetic polymers and/or natural polymers having hydrophilic groups dissolved in (a) and shows **viscosity** 50,000-1,500,000 cPs at 23.degree. and 1 rpm using a conversion const. 1.61 .times. 104. Porcelain powder (av. particle size 10 .mu.m, softening point 700.degree.), prepd. by milling and crystg. glass (prepd. from feldspar, silica stone, and inorg. salts) and milling again, was kneaded with a binder (**viscosity** 552,000 cPs) contg. 97.5% H2O and 2.5% ammonium polyacrylate at 71:29 at 23.degree. for 20 min to give a porcelain paste. Workability of the paste and properties of the porcelain prepd. from the paste were examd.

LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001079019	A2	20010327	JP 1999-261427	19990916
GB 2355266	A1	20010418	GB 2000-22340	20000912
US 6444597	B1	20020903	US 2000-662140	20000914
DE 10045663	A1	20010523	DE 2000-10045663	20000915

PRIORITY APPLN. INFO.: JP 1999-261427 A 19990916

AB The paste, which are easily handled by unskilled dental technicians and used for making dental porcelain such as crowns, comprises 7-45 wt. parts binder and porcelain powder balance, and the binder contains (a) .gtoreq.1 org. solvents selected from di- or trihydric alcs., hydroxy-contg. ethers, and hydroxy(meth)acrylates and/or H2O and (b) synthetic polymers and/or natural polymers having hydrophilic groups dissolved in (a) and shows **viscosity** 50,000-1,500,000 cPs at 23.degree. and 1 rpm using a conversion const. 1.61 .times. 104. Porcelain powder (av. particle size 10 .mu.m, softening point 700.degree.), prepd. by milling and crystg. glass (prepd. from feldspar, silica stone, and inorg. salts) and milling again, was kneaded with a binder (**viscosity** 552,000 cPs) contg. 97.5% H2O and 2.5% ammonium polyacrylate at 71:29 at 23.degree. for 20 min to give a porcelain paste. Workability of the paste and properties of the porcelain prepd. from the paste were examd.

L14 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:861512 CAPLUS
DOCUMENT NUMBER: 134:32938
TITLE: Keratinocyte Growth Factor-2 formulations
INVENTOR(S): Gentz, Reiner L.; Chopra, Arvind; Kaushal, Parveen; Spitznagel, Thomas; Unsworth, Edward; Khan, Fazal
PATENT ASSIGNEE(S): Human Genome Sciences, Inc., USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072872	A1	20001207	WO 2000-US15186	20000602
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1196187	A1	20020417	EP 2000-941186	20000602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003500456	T2	20030107	JP 2000-620980	20000602

PRIORITY APPLN. INFO.: US 1999-137448P P 19990602
US 1999-160913P P 19991022
WO 2000-US15186 W 20000602

AB The invention is directed to liq. and lyophilized forms of Keratinocyte Growth Factor-2 (KGF-2) and derivs. thereof. This invention further relates to the formulations of KGF-2 for therapeutic use, for example, to promote or accelerate wound healing.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:116749 CAPLUS
DOCUMENT NUMBER: 132:156550
TITLE: High **viscosity** make-up composition containing an aqueous polymer dispersion
INVENTOR(S): Bara, Isabelle; Jager-Lezer, Nathalie
PATENT ASSIGNEE(S): L'Oreal, Fr.
SOURCE: Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 979642	A1	20000216	EP 1999-401776	19990715
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
FR 2782267	A1	20000218	FR 1998-10332	19980812
FR 2782267	B1	20010511		
BR 9903433	A	20000926	BR 1999-3433	19990802
JP 2000063240	A2	20000229	JP 1999-228059	19990811

PRIORITY APPLN. INFO.: FR 1998-10332 A 19980812
AB A cosmetic compn. contains an aq. polymer dispersion, and a thickening agent q.s. to give a **viscosity** of .gtoreq.4.5 and .ltoreq.1000 Pa.s at 25.degree.. A cosmetic compn. contained Sancure 861 (an aq. dispersion of polyurethane) 75, Serad FX1100 (a polyurethane) 3, pigment 5, ethanol 7, preservatives q.s., and water q.s. 100%.
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:558999 CAPLUS
DOCUMENT NUMBER: 132:166954
TITLE: Automated characterization of polymer solutions
AUTHOR(S): Strelitzki, Roland; Reed, Wayne F.
CORPORATE SOURCE: Department of Physics, Tulane University, New Orleans, LA, 70118, USA
SOURCE: Polymer Preprints (American Chemical Society, Division of Polymer Chemistry) (1999), 40(2), 663-664
CODEN: ACPPAY; ISSN: 0032-3934
PUBLISHER: American Chemical Society, Division of Polymer Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This paper describes the application of automated measurements (by means of static light scattering and viscometry) of wt.-av. mol. wt., root mean square radius of gyration, second and third virial coeffs., and reduced **viscosity** using continuous dilns. for aq. poly(vinylpyrrolidone) and **hyaluronic acid**.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:639516 CAPLUS
DOCUMENT NUMBER: 111:239516
TITLE: Stable lyophilized formulations containing growth factors
INVENTOR(S): Finkenaur, Amy L.; Cohen, Jonathan M.
PATENT ASSIGNEE(S): Ethicon, Inc., USA
SOURCE: Eur. Pat. Appl., 11 pp.

CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 308238	A1	19890322	EP 1988-308573	19880916
R: AT, BE, CH, DE, ES, FR, GB, IT, LI, LU, NL, SE				
AU 8822236	A1	19890323	AU 1988-22236	19880914
DK 8805167	A	19890319	DK 1988-5167	19880916
JP 01121223	A2	19890512	JP 1988-232101	19880916
ZA 8806943	A	19900530	ZA 1988-6943	19880916

PRIORITY APPLN. INFO.: US 1987-98817 19870918

AB A stable lyophilized compn. comprises a polypeptide growth factor having human mitogenic or angiogenic activity and a water-sol. or water-swellable polymer capable of imparting **viscosity** to a reconstituted soln. of the compn. A compn. contg. EGF 50 .mu.g and mannitol 50 mg was lyophilized by freezing at -55.degree. at 1 atm for 4 h, -25.degree. at 1 atm for 4 h, and -55.degree. for 0.5 h at full vacuum. The lyophilized cake was stable for at least 209 days at 37.degree..

L14 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:540911 CAPLUS
DOCUMENT NUMBER: 107:140911
TITLE: Cosmetics containing acylated lysines and polymers
INVENTOR(S): Mori, Kunihiko; Kawai, Mitsuo
PATENT ASSIGNEE(S): Pola Chemical Industries, Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62126107	A2	19870608	JP 1985-266779	19851127

PRIORITY APPLN. INFO.: JP 1985-266779 19851127

AB A film-forming cosmetic contains (1) N-acylated lysine 0.01-5.0, (2) a water-sol. polymer 0.05-20.0, and (3) H2O or an EtOH soln. 50-99% by wt. (**viscosity**, .gtoreq.3000 cP). The acylated lysines are R1NH(CH2)4CH(NHR2)CO2H (R1 and R2 = H or C8-22 acyl and at least one of these Rs is acyl) such as N-(2-ethylhexyl)lysine. The polymer is poly(acrylic acid), poly(methacrylic acid), **polyvinylpyrrolidone** , or their derivs. This cosmetic applied to the skin is not washed off by perspiration or body fluids excreted from the skin. Thus, an eye liner was prepd. consisting of microcryst. wax 2, beeswax 8, fatty acid sorbitan esters 2, polyoxyethylene sorbitan fatty acid ester 2, Et cellulose 2, Arabic gum 1, a dye 10, H2O 72.9, and N-lauroyllysine 0.1 part by wt.

L14 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1987:540911 CAPLUS
DOCUMENT NUMBER: 107:140911
TITLE: Cosmetics containing acylated lysines and polymers
INVENTOR(S): Mori, Kunihiko; Kawai, Mitsuo
PATENT ASSIGNEE(S): Pola Chemical Industries, Inc., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 7 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 62126107	A2	19870608	JP 1985-266779	19851127

PRIORITY APPLN. INFO.: JP 1985-266779 19851127

AB A film-forming cosmetic contains (1) N-acylated lysine 0.01-5.0, (2) a water-sol. polymer 0.05-20.0, and (3) H2O or an EtOH soln. 50-99% by wt. (**viscosity**, .gtoreq.3000 cP). The acylated lysines are R1NH(CH2)4CH(NHR2)CO2H (R1 and R2 = H or C8-22 acyl and at least one of these Rs is acyl) such as N-(2-ethylhexyl)lysine. The polymer is poly(acrylic acid), poly(methacrylic acid), **polyvinylpyrrolidone** , or their derivs. This cosmetic applied to the skin is not washed off by perspiration or body fluids excreted from the skin. Thus, an eye liner was prepd. consisting of microcryst. wax 2, beeswax 8, fatty acid sorbitan esters 2, polyoxyethylene sorbitan fatty acid ester 2, Et cellulose 2, Arabic gum 1, a dye 10, H2O 72.9, and N-lauroyllysine 0.1 part by wt.

L19 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107048 CAPLUS
DOCUMENT NUMBER: 136:156435
TITLE: Pharmaceutical compositions for the treatment of inflammatory and ulcerative conditions of moist epithelial surfaces such as mucositis, stomatitis and Behcet's syndrome
INVENTOR(S): Mastrodonato, Marco
PATENT ASSIGNEE(S): Sinclair Pharma S.r.l., Italy
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009637	A2	20020207	WO 2001-EP8303	20010718
WO 2002009637	A3	20021205		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
AU 2002012113	A5	20020213	AU 2002-12113	20010718

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
WO 2001-EP8303 W 20010718

AB Pharmaceutical compns. comprising as active ingredients EDs of **hyaluronic acid**, glycyrrhetinic acid and **polyvinylpyrrolidone**, for the treatment of painful, inflammatory and ulcerative conditions of moist epithelial surfaces such as mucositis and Behcet's syndrome. Thus, a formulation contained sodium hyaluronate 0.1, glycyrrhetinic acid 0.06, PVP 9.0, maltodextrin 6.00, propylene glycol 2.94, potassium sorbate 0.3, sodium benzoate 0.3, hydroxyethyl cellulose 1.5, hydrogenated castor oil PEG-40 0.27, disodium EDTA 0.1, benzalkonium chloride 0.5, perfume (Glycyrrhiza ext.) 0.16, sodium saccharin 0.1, and water 78.44%.

L19 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:755211 CAPLUS
DOCUMENT NUMBER: 133:340208
TITLE: Novel compositions useful for delivering anti-inflammatory agents into a cell
INVENTOR(S): Unger, Evan C.; McCreery, Thomas; Sadewasser, David A.
PATENT ASSIGNEE(S): ImaRx Pharmaceutical Corp., USA
SOURCE: Eur. Pat. Appl., 78 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1046394	A2	20001025	EP 2000-303249	20000418
EP 1046394	A3	20011010		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,

IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.: US 1999-294623 A 19990419
AB The present invention is directed, inter alia, to compns. and their use for delivering compds. into a cell. In a preferred embodiment, the compns. comprise, in combination with the compd. to be delivered, an org. halide, a targeting ligand, and a nuclear localization sequence, optionally in the presence of a carrier. Ultrasound may be applied, if desired. The compns. are particularly suitable for the treatment of inflammatory diseases.

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1976:499131 CAPLUS
DOCUMENT NUMBER: 85:99131
TITLE: Search for an artificial lubricant for joints based on complexes of poly(vinyl chloride) with **hyaluronic acid** biopolymers
AUTHOR(S): Vasilionkaitis, V.
CORPORATE SOURCE: Nauchno-Issled. Inst. Eksp. Klin. Med., Vilnius, USSR
SOURCE: Sint. Izuch. Fiziol. Akt. Veshchestv, Tezisy Dokl. Mezhvuz Nauchn. Konf. Uchastiem Farmakol. Latv. Est. SSR (1975), 20-1. Vil'nyus. Gos. Univ.: Vilnius, USSR.
CODEN: 33GOAY
DOCUMENT TYPE: Conference
LANGUAGE: Russian
AB An aq. soln. of **polyvinylpyrrolidone** (PVP) applied to the joints of rabbits with the exptl. arthritis or osteoartherosis exerted local **antiinflammatory** action, decreased the activity of degrading enzymes in the joint cartilage, normalized permeability of the synovial membrane, and improved the functioning of the joints. A complex of PVP with **hyaluronic acid** similarly applied inhibited the development of osteoarthritis and increased the total no. and individual fractions of serum sulfopolysaccharides. Possible clin. use of these prepns. as lubricants for artificial joints is considered.

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(FILE 'HOME' ENTERED AT 16:52:13 ON 08 MAY 2003)

FILE 'CAPLUS' ENTERED AT 16:52:27 ON 08 MAY 2003
L1 0 S HYALURONIC ADJ ACID
L2 11020 S HYALURONIC ACID
L3 92 S L2 AND POLYVINYLPYRROLIDONE
L4 42 S L3 AND WATER
L5 17 S L3 AND AQUEOUS
L6 7 S L4 AND VISCOSITY
L7 0 S L6 AND CENTIPOISE
L8 8 S L4 AND GEL
L9 7 S L8 NOT L6
L10 2 S L4 AND GLYCYRRHETINIC ACID
L11 14 S L4 AND ACRYLIC
L12 2 S L11 AND ANTIBACTERIAL
L13 2 S L3 AND GLYCYRRHETINIC ACID
L14 9 S L3 AND VISCOSITY
L15 1 S L14 AND ANTI-INFLAMMATORY
L16 1 S L14 AND ANTIINFLAMMATORY
L17 27 S L3 AND SURFACTANT
L18 0 S L3 AND ANTIINFLAMATORY
L19 3 S L3 AND ANTIINFLAMMATORY

L19 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1976:499131 CAPLUS

DOCUMENT NUMBER: 85:99131

TITLE: Search for an artificial lubricant for joints based on complexes of poly(vinyl chloride) with **hyaluronic acid** biopolymers

AUTHOR(S): Vasilionkaitis, V.

CORPORATE SOURCE: Nauchno-Issled. Inst. Eksp. Klin. Med., Vilnius, USSR

SOURCE: Sint. Izuch. Fiziol. Akt. Veshchestv, Tezisy Dokl. Mezhvuz Nauchn. Konf. Uchastiem Farmakol. Latv. Est. SSR (1975), 20-1. Vil'nyus. Gos. Univ.: Vilnius, USSR.
CODEN: 33GOAY

DOCUMENT TYPE: Conference

LANGUAGE: Russian

AB An aq. soln. of **polyvinylpyrrolidone** (PVP) applied to the joints of rabbits with the exptl. arthritis or osteoartherosis exerted local **antiinflammatory** action, decreased the activity of degrading enzymes in the joint cartilage, normalized permeability of the synovial membrane, and improved the functioning of the joints. A complex of PVP with **hyaluronic acid** similarly applied inhibited the development of osteoarthritis and increased the total no. and individual fractions of serum sulfopolysaccharides. Possible clin. use of these prepns. as lubricants for artificial joints is considered.

L21 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:281958 CAPLUS
DOCUMENT NUMBER: 138:292774
TITLE: Drug delivery device with protective separating layer
INVENTOR(S): Shanley, John F.; Parker, Theodore L.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp., Cont.-in-part of U.S. Ser. No. 948,989.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003068355	A1	20030410	US 2002-253020	20020923
US 2002082680	A1	20020627	US 2001-948989	20010907

PRIORITY APPLN. INFO.: US 2001-314259P P 20010820
US 2001-948989 A2 20010907
US 2000-688092 A2 20001016

AB The present invention relates to implantable medical devices for delivery of drugs to a patient. More particularly, the invention relates to a device having the drugs protected by a protective layer that prevents or retards processes that deactivate or degrade the active agents. Thus, a mixt. of poly(lactide-co-glycolide) (PLGA) 7% by wt. and a suitable org. solvent, such as DMSO, NMP, or DMAC 93% is prepd. The mixt. is loaded dropwise into holes in the stent, then the solvent is evapd. to begin formation of the barrier layer. A second barrier layer is laid over the first by the same method of filling polymer soln. into the hole followed by solvent evapn. The process is continued until 5 individual layers have been laid down to form the barrier layer. A second mixt. of a limus, such as sirolimus, 3% solid basis, and dipalmitoylphosphatidylcholine 7% solid basis in DMSO is introduced into holes in the stent over the barrier layer. The solvent is evapd. to form a drug filled protective layer and the filling and evapn. procedure repeated until the hole is filled to about 75% of its total vol. with drug in protective layer layered on top of the barrier layer.

L21 ANSWER 2 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:5754 CAPLUS
DOCUMENT NUMBER: 138:61349
TITLE: Hydration compositions containing a polymeric matrix for corneal pre-surgery treatment
INVENTOR(S): Sacharoff, Alex
PATENT ASSIGNEE(S): Alcon, Inc., Switz.
SOURCE: PCT Int. Appl., 18 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000231	A1	20030103	WO 2002-US19784	20020621

W: AU, BR, CA, JP, KR, US, ZA
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

PRIORITY APPLN. INFO.: US 2001-300227P P 20010622

AB Compns. and methods for corneal tissue treatment prior to surgery are disclosed. It has been discovered that an important factor contributing to the variance between predicted and actual results in both photoablation

and mech. resection of corneal tissue is the degree of hydration of the tissue, particularly the degree of hydration in the surface layers of tissue. The compns. of the invention contain a polymeric matrix, e.g., a polysaccharide, and a hydration fluid, the fluid being held in the matrix by a predefined osmotic pressure (250-350 mOsm/kg) such that upon application of the compn. to the corneal surface, a standardized level of hydration is achieved in the corneal tissue by fluid transfer between the matrix and the tissue.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:928236 CAPLUS
DOCUMENT NUMBER: 138:315
TITLE: Compositions and methods using **hyaluronic acid** and **polyvinylpyrrolidone** for the treatment or prevention of inflammation
INVENTOR(S): Mastrodonato, Marco; Braguti, Gianluca
PATENT ASSIGNEE(S): Pennie + Edmonds Llp, Italy
SOURCE: U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 80,624.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002183278	A1	20021205	US 2002-80736	20020222
IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
US 2002173485	A1	20021121	US 2002-80624	20020221

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
US 2002-80624 A2 20020221

AB The present invention relates to compds. contg. as active ingredients **hyaluronic acid** and **polyvinylpyrrolidone**, for the treatment of **inflammatory**, ulcerative and painful conditions of moist epithelial surfaces such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, and Behcet's syndrome.

L21 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:716325 CAPLUS
DOCUMENT NUMBER: 137:246551
TITLE: Pharmaceutical compositions comprising crystals of polymeric carrier-stabilized antibodies and fragments for therapeutic uses
INVENTOR(S): Shenoy, Bhami; Govardhan, Chandrika P.; Yang, Mark X.; Margolin, Alexey L.
PATENT ASSIGNEE(S): Altus Bioloigics Inc., USA
SOURCE: PCT Int. Appl., 173 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002072636	A2	20020919	WO 2001-US49628	20011226

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2002136719 A1 20020926 US 2001-34950 20011226
PRIORITY APPLN. INFO.: US 2000-258704P P 20001228

AB Methods are also provided for prepg. stabilized formulations of whole antibody crystals or antibody fragment crystals using pharmaceutical ingredients or excipients and optionally encapsulating the crystals or crystal formulations in a polymeric carrier to produce compns. and using such protein crystals for biomedical applications, including delivery of therapeutic proteins and vaccines. Antibodies prepd. were Rituximab, Infliximab, Abciximab, Palivizumab, Murumonab-CD3, Gemtuzumab, Trastuzumab, Basiliximab, Daclizumab, Etanercept, and Ibritumomab tiuxetan. These antibody prepns. are useful for treating cardiovascular disease, respiratory disease, transplant rejection, cancer, **inflammatory** disease, and for radioimmunotherapy.

L21 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107048 CAPLUS
DOCUMENT NUMBER: 136:156435
TITLE: Pharmaceutical compositions for the treatment of **inflammatory** and ulcerative conditions of moist epithelial surfaces such as mucositis, stomatitis and Behcet's syndrome
INVENTOR(S): Mastrodonato, Marco
PATENT ASSIGNEE(S): Sinclair Pharma S.r.l., Italy
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009637	A2	20020207	WO 2001-EP8303	20010718
WO 2002009637	A3	20021205		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
AU 2002012113	A5	20020213	AU 2002-12113	20010718

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
WO 2001-EP8303 W 20010718

AB Pharmaceutical compns. comprising as active ingredients EDs of **hyaluronic acid**, glycyrrhetinic acid and **polyvinylpyrrolidone**, for the treatment of painful, **inflammatory** and ulcerative conditions of moist epithelial surfaces such as mucositis and Behcet's syndrome. Thus, a formulation contained sodium hyaluronate 0.1, glycyrrhetinic acid 0.06, PVP 9.0, maltodextrin 6.00, propylene glycol 2.94, potassium sorbate 0.3, sodium benzoate 0.3, hydroxyethyl cellulose 1.5, hydrogenated castor oil PEG-40 0.27, disodium EDTA 0.1, benzalkonium chloride 0.5, perfume (Glycyrrhiza ext.) 0.16, sodium saccharin 0.1, and water 78.44%.

L21 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:472523 CAPLUS
DOCUMENT NUMBER: 135:66255
TITLE: Liquid composition of a biodegradable block copolymer for drug delivery system
INVENTOR(S): Seo, Min-hyo; Choi, In-ja
PATENT ASSIGNEE(S): Samyang Corp., S. Korea
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001045742	A1	20010628	WO 2000-KR1508	20001221
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1244471	A1	20021002	EP 2000-989005	20001221
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003082234	A1	20030501	US 2002-169012	20020622

PRIORITY APPLN. INFO.: KR 1999-60349 A 19991222
WO 2000-KR1508 W 20001221

AB The present invention relates to a liq. polymeric compn. capable of forming a physiol. active substance-contg. implant when it is injected into a living body and a method of prepn. The compn. comprises a water-sol. biocompatible liq. polyethylene glycol deriv., a biodegradable block copolymer which is insol. in water but sol. in the water-sol. biocompatible liq. polyethylene glycol deriv. and a physiol. active substance. Thus, a triblock copolymer was prepd. from lactide-1,4-dioxanone and PEG. Piroxicam 150, the above biodegradable block copolymer 400, diacetyl polyethylene glycol 420, and gelatin 30 mg were dissolved in a 50% aq. HOAc soln. and the drug-contg. liq. polymeric compn. was filtered and the org. solvent was removed.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 7 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:300486 CAPLUS
DOCUMENT NUMBER: 134:331616
TITLE: Sustained release microspheres based on a carrier protein, a water soluble polymer and complexing agents
INVENTOR(S): Scott, Terrence L.; Brown, Larry R.; Riske, Frank J.; Blizzard, Charles D.; Rashba-Step, Julia
PATENT ASSIGNEE(S): Epic Therapeutics, Inc., USA
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028524	A1	20010426	WO 2000-US28200	20001012
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6458387	B1	20021001	US 1999-420361	19991018
EP 1223917	A1	20020724	EP 2000-973477	20001012
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
US 2003059474	A1	20030327	US 2002-245776	20020917

PRIORITY APPLN. INFO.: US 1999-420361 A 19991018
WO 2000-US28200 W 20001012

AB A microsphere compn. for sustained release of therapeutic or diagnostic agents comprises (1) a carrier protein, (2) a water-sol. polymer, (3) a polyanionic polysaccharide as a first complexing agent, and (4) a divalent metal cation (Ca and Mg) as a second complexing agent. The microspheres have a smooth surface that includes a plurality of channel openings that are < 1000 .ANG. in diam. Various drugs were encapsulated into microspheres. For example, microspheres contg. leuprolide acetate were prepd. using human serum albumin (HSA), dextran sulfate, polyethylene glycol, and **polyvinylpyrrolidone**. The microspheres were composed of approx. 10% leuprolide acetate, 50% human serum albumin, 20% dextran sulfate and 20% polyethylene glycol/**polyvinylpyrrolidone**. Similar particles were prepd. which also included zinc sulfate or caprylic acid, both of which retarded the release of protein and peptide from the microspheres. Also, rifampicin-contg. HSA microspheres were prepd. with HSA incorporation of 74% and rifampicin incorporation into the particles of > 6.8%. The av. size of the particles was detd. to be 68 nm in diam.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:755211 CAPLUS
DOCUMENT NUMBER: 133:340208
TITLE: Novel compositions useful for delivering anti-**inflammatory** agents into a cell
INVENTOR(S): Unger, Evan C.; McCreery, Thomas; Sadewasser, David A.
PATENT ASSIGNEE(S): ImaRx Pharmaceutical Corp., USA
SOURCE: Eur. Pat. Appl., 78 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1046394	A2	20001025	EP 2000-303249	20000418
EP 1046394	A3	20011010		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1999-294623 A 19990419

AB The present invention is directed, inter alia, to compns. and their use for delivering compds. into a cell. In a preferred embodiment, the compns. comprise, in combination with the compd. to be delivered, an org. halide, a targeting ligand, and a nuclear localization sequence, optionally in the presence of a carrier. Ultrasound may be applied, if desired. The compns. are particularly suitable for the treatment of **inflammatory** diseases.

L21 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:755211 CAPLUS
DOCUMENT NUMBER: 133:340208
TITLE: Novel compositions useful for delivering anti-**inflammatory** agents into a cell
INVENTOR(S): Unger, Evan C.; McCreery, Thomas; Sadewasser, David A.
PATENT ASSIGNEE(S): ImaRx Pharmaceutical Corp., USA
SOURCE: Eur. Pat. Appl., 78 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1046394	A2	20001025	EP 2000-303249	20000418
EP 1046394	A3	20011010		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: US 1999-294623 A 19990419

AB The present invention is directed, inter alia, to compns. and their use for delivering compds. into a cell. In a preferred embodiment, the compns. comprise, in combination with the compd. to be delivered, an org. halide, a targeting ligand, and a nuclear localization sequence, optionally in the presence of a carrier. Ultrasound may be applied, if desired. The compns. are particularly suitable for the treatment of **inflammatory** diseases.

L21 ANSWER 9 OF 9 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:456858 CAPLUS
DOCUMENT NUMBER: 133:94512
TITLE: Improved formulation for topical non-invasive application in vivo
INVENTOR(S): Cevc, Gregor
PATENT ASSIGNEE(S): Idea Innovative Dermale Applikationen G.m.b.H., Germany
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000038653	A1	20000706	WO 1998-EP8421	19981223
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2356080	AA	20000706	CA 1998-2356080	19981223
AU 9925137	A1	20000731	AU 1999-25137	19981223
EP 1140021	A1	20011010	EP 1998-966846	19981223
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9816113	A	20011023	BR 1998-16113	19981223
JP 2002533379	T2	20021008	JP 2000-590607	19981223
EE 200100342	A	20021015	EE 2001-200100342	19981223
NO 2001003164	A	20010822	NO 2001-3164	20010622
US 2002064524	A1	20020530	US 2001-887493	20010622

PRIORITY APPLN. INFO.: WO 1998-EP8421 A 19981223
OTHER SOURCE(S): MARPAT 133:94512

AB A formulation comprises mol. arrangements capable of penetrating pores in a barrier, owing to penetrant adaptability, despite the fact that the av. diam. of the pores is smaller than the av. penetrant diam., provided that the penetrants can transport agents or cause permeation through the pores after penetrants have entered pores. The formulation comprises at least 1 consistency builder in an amt. that increases the formulation to maximally 5 Nm/s so that spreading over is enabled. The formulation also contains 1 antioxidant in an amt. that reduces the increase of oxidn. index to <100% per 6 mo and/or at least 1 microbicide in an amt. that reduces the bacterial count of 1 million germs added/g of total mass of the formulation to <100 in the case of aerobic bacteria, to <10 in the case of entero-bacteria, and to <1 in the case of Pseudomonas aeruginosa or Staphilococcus aureus, after a period of 4 days. Thus, a compn. contained soybean phosphatidylcholine 347, Tween-80 623, sodium dodecyl sulfate 30, benzyl alc. 50, clobetasol 17-propionate 25 and pH 6.5 50 mM phosphate buffer 9000 mg.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:928236 CAPLUS
DOCUMENT NUMBER: 138:315
TITLE: Compositions and methods using **hyaluronic acid** and **polyvinylpyrrolidone** for the treatment or prevention of inflammation
INVENTOR(S): Mastrodonato, Marco; Braguti, Gianluca
PATENT ASSIGNEE(S): Pennie + Edmonds Llp, Italy
SOURCE: U.S. Pat. Appl. Publ., 9 pp., Cont.-in-part of U.S. Ser. No. 80,624.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002183278	A1	20021205	US 2002-80736	20020222
IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
US 2002173485	A1	20021121	US 2002-80624	20020221

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
US 2002-80624 A2 20020221

AB The present invention relates to compds. contg. as active ingredients **hyaluronic acid** and **polyvinylpyrrolidone**, for the treatment of inflammatory, ulcerative and painful conditions of moist epithelial surfaces such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, and Behcet's syndrome.

L10 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107048 CAPLUS
DOCUMENT NUMBER: 136:156435
TITLE: Pharmaceutical compositions for the treatment of inflammatory and ulcerative conditions of moist epithelial surfaces such as mucositis, stomatitis and Behcet's syndrome
INVENTOR(S): Mastrodonato, Marco
PATENT ASSIGNEE(S): Sinclair Pharma S.r.l., Italy
SOURCE: PCT Int. Appl., 9 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002009637	A2	20020207	WO 2001-EP8303	20010718
WO 2002009637	A3	20021205		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

IT 2000MI1732	A1	20020128	IT 2000-MI1732	20000728
AU 2002012113	A5	20020213	AU 2002-12113	20010718

PRIORITY APPLN. INFO.: IT 2000-MI1732 A 20000728
WO 2001-EP8303 W 20010718

AB Pharmaceutical compns. comprising as active ingredients EDs of

hyaluronic acid, **glycyrrhetinic acid**
and **polyvinylpyrrolidone**, for the treatment of painful,
inflammatory and ulcerative conditions of moist epithelial surfaces such
as mucositis and Behcet's syndrome. Thus, a formulation contained sodium
hyaluronate 0.1, **glycyrrhetinic acid** 0.06, PVP 9.0,
maltodextrin 6.00, propylene glycol 2.94, potassium sorbate 0.3, sodium
benzoate 0.3, hydroxyethyl cellulose 1.5, hydrogenated castor oil PEG-40
0.27, disodium EDTA 0.1, benzalkonium chloride 0.5, perfume (Glycyrrhiza
ext.) 0.16, sodium saccharin 0.1, and **water** 78.44%.

=> d his

(FILE 'HOME' ENTERED AT 16:52:13 ON 08 MAY 2003)

FILE 'CAPLUS' ENTERED AT 16:52:27 ON 08 MAY 2003

L1	0	S	HYALURONIC ADJ ACID
L2	11020	S	HYALURONIC ACID
L3	92	S	L2 AND POLYVINYLPYRROLIDONE
L4	42	S	L3 AND WATER
L5	17	S	L3 AND AQUEOUS
L6	7	S	L4 AND VISCOSITY
L7	0	S	L6 AND CENTIPOISE
L8	8	S	L4 AND GEL
L9	7	S	L8 NOT L6
L10	2	S	L4 AND GLYCYRRHETINIC ACID

US 20020173485A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2002/0173485 A1

Mastradonato et al. (43) Pub. Date: Nov. 21, 2002

(54) COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF INFLAMMATION

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(21) Appl. No.: 10/080,624

(22) Filed: Feb. 21, 2002

(30) Foreign Application Priority Data

Jul. 28, 2000 (IT) ..... MI 2000 A 001732

Publication Classification

(51) Int. Cl.[7] A61K 31/728; A61K 9/14

(52) U.S. Cl. 514/54; 424/486

(57) ABSTRACT

The present invention relates to compounds containing as active ingredients hyaluronic acid and polyvinylpyrrolidone, for the treatment of inflammatory, ulcerative and painful conditions of moist epithelial surfaces such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, and Behcet's syndrome.

COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF INFLAMMATION

[0001] The present application claims priority benefits of International Patent Application No. PCT/EP01/08303 filed Jul. 18, 2001, (published as WO 02/09637 in English on Feb. 7, 2002), which in turn claims priority benefits of Italian Patent Application No. MI 2000 A 001732, filed Jul. 28, 2000, the disclosures of each of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] This invention relates to certain compositions useful for the management of painful ulcerative and inflammatory conditions of moist surfaces including the mouth, oropharynx, oesophagus, vagina and rectum (including, but not limited to, mucositis, stomatitis, aphthous ulcerations, and Behcet's syndrome).

BACKGROUND OF THE INVENTION

[0003] Aggressive cancer treatment may have toxic effects on normal cells as well as cancer cells. The gastrointestinal tract, including the mouth, is especially affected because these cells are replaced by the body continuously.

[0004] Mucositis, an inflammation of the mucous membranes in the mouth, is one of the most common oral problems occurring after chemotherapy and radiation therapy. Mucositis can contribute to oral infections, inability to taste normally and pain arising from the resulting open sores that can develop. Mucositis can become so painful that the patient will not eat or drink, contributing to dehydration and malnutrition.

[0005] Radiation therapy to the head and neck for cancers in those areas commonly injure saliva glands and the inside of the mouth which can cause dry mouth, leading to dental disease.

[0006] The mucositis problem is not restricted to cancer patients, as mucositis frequently also occurs in HIV patients, particularly when associated with Kaposi's sarcoma, in patients affected with non-Hodgkin's lymphoma, in debilitated elderly patients and in patients receiving BRM treatments like interleukin-2, TNF, interferons, lymphokine-activated lymphocytes and the like.

[0007] Such oral problems may make it difficult for the cancer or AIDS patient to receive a complete dose of chemotherapy or radiation therapy. Sometimes treatment must be stopped completely. Such problems are not infrequent: about half of the patients have severe oral lesions that require medical intervention, mostly involving the changes in cancer medication or treatment mentioned above.

[0008] Current therapies for mucositis are limited. Cleaning the mouth is recommended to retard the progression of the condition.

[0009] Oral cleaning care includes gently cleaning the mouth, moisturizing the lips and mouth, and relieving pain and swelling. A soft toothbrush or toothette cleans teeth well and gently. Cleansing agents can include "salt and soda" (½ tsp. salt and 2 Tbs. of sodium bicarbonate in 32 oz. of warm water), normal saline, sterile water, or sodium bicarbonate (1 tsp. in 8 oz of water). Hydrogen peroxide diluted in equal amounts of water or weak salt water can be used when crusting is present. (This should be used for 1 or 2 days only because it will keep mucositis from healing.) Gentle wiping with a wet gauze dipped in salt water helps remove particles. Toothettes may be too rough for some areas. Particles should be removed before ointments or other medications are put onto the gums or tissues. Rinsing often cleans and moistens the tissues, prevents crusting, and soothes sore gums and tissues. Frequent rinsing prevents particles and bacteria from collecting in the mouth. A salt and baking soda solution neutralizes acids and dissolves thick saliva.

[0010] Capsaicin, the active ingredient in hot peppers, reportedly has used to increase a person's ability to tolerate pain. When capsaicin is put on inflamed tissues in the mouth, mucositis pain may decrease as the burning feeling from the capsaicin decreases. Capsaicin is only being used experimentally; however, all side effects are not known.

[0011] Mostly, physicians have resorted ice chips or to rather makeshift mixtures of benzocaine with kaopectate and the like. These approaches provide rather limited, temporary relief.

[0012] Carrington Laboratories of Irving, Tex. has sold a mucositis product called "Radiacare" for a number of years. However, this product has made limited inroads into the marketplace, and thus has provided few patients relief from the symptoms of mucositis.

[0013] Many women get oral aphthous ulceration at specific times of the menstrual cycle and simultaneously get the same kind of ulcers in the genital tract, in particular the vulva and vagina. This is sometimes very severe and can cause retention of urine and require strong painkillers and sedatives. The most severe form is called Behcet's syndrome.

[0014] The terms mucositis and stomatitis are often used interchangeably but may include some general distinctions. Mucositis describes a toxic inflammatory reaction affecting the gastrointestinal tract, which may result from exposure to chemotherapeutic agents or ionising radiation. Mucositis typically manifests as an erythematous, burn-like lesion or as random, focal-to-diffuse, ulcerative lesions. Stomatitis refers to an inflammatory reaction affecting the oral mucosa, with or without ulceration, that may be caused or intensified by pharmacological, particularly chemotherapeutic treatments, or by radiotherapy. Stomatitis can range from mild to severe; the patient with severe stomatitis is unable to take anything by mouth.

[0015] Thus, there is a clear need for compositions and methods useful for treating or preventing inflammation, including but not limited to, mucositis, stomatitis, aphthous ulcerations, Behcet's syndrome, etc.

[0016] Citation of a reference in this or any section of the specification shall not be construed as an admission that such reference is prior art to the present invention.

SUMMARY OF THE INVENTION

[0017] The present invention is directed to a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 and 2.2 million daltons; from about 0.04 to about 15% by weight of

a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about K85 to about K95 and is from about 3 to about 10% by weight of the composition. In another embodiment, the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about 7 to about 10% by weight of the composition. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons, and from about 0.01 to about 2% by weight of the composition, and wherein the viscosity of the composition is from about 90 to about 1000 centipoise. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01% to about 2% by weight of the composition, and wherein the viscosity of the composition is from about 90 to about 1000 centipoise. In a preferred embodiment, the composition is in the form of a gel.

[0018] The present invention is also directed to a composition comprising from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, with a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment, the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about K85 to about K95, and is from about 6 to about 12% by weight of the composition. In another embodiment, the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about 8 to about 10% by weight of the composition. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition. In a preferred embodiment, the composition is in the form of a gel.

[0019] The present invention is also directed to a flexible packet comprising a composition comprising from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, with a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In a preferred embodiment, the packet is a sealed pouch comprising from about 10 to about 30 milliliters of the composition.

[0020] The present invention is also directed to a composition comprising hyaluronic acid, or a pharmaceutically acceptable salt thereof, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof. In an embodiment, the composition further comprises a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavor, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer. The composition may also further comprise a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame. In yet another embodiment, the composition further comprises an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

[0021] The present invention is also directed to a method for treating or preventing inflammation in a patient comprising administering to a patient in need thereof an effective amount of a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment, the composition is administered at least twice daily for at least two consecutive days. In yet another embodiment, the composition is administered at least three times daily for at least four consecutive days.

[0022] The present invention is also directed to a method for treating or preventing inflammation in a patient, comprising administering to a patient in need thereof an effective amount of a composition comprising hyaluronic acid, or a pharmaceutically acceptable salt thereof, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof. In addition to its ordinary meaning, the term treatment encompasses inhibition of progression of symptoms or amelioration of symptoms of inflammation and mucositis.

[0023] The present invention can be more fully explained by reference to the following detailed description and illustrative examples.

DETAILED DESCRIPTION OF THE INVENTION

[0024] Surprisingly, the topical administration of a formulation comprising an effective amount of hyaluronic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof, provides an effective therapeutical or preventive treatment for mucositis and stomatitis of various origin and severity and, more generally, of the lesions of the oropharynx cavity and oesophagus, particularly those caused by dental devices and by radio- or chemotherapy.

[0025] Without being bound by a particular mode of action, the favorable therapeutic results obtained by the use of the compositions of the present invention are believed to be due to both the interactions between hyaluronic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof, and the capability of the formulation of adhering to the oral mucosa providing a protective coating for the exposed nerve endings, and thus, reduction of pain and promoting cicatrisation and healing of the lesions. Furthermore, it is believed that the moisturizing effect of the

compositions has beneficial effect as it protects mucous membranes from further irritating lesions.

[0026] In one embodiment, the present invention involves a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof, and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise.

[0027] In an alternative embodiment, the present invention involves a composition comprising from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. The compositions of the present invention can be diluted with water, and accordingly, is useful for obtaining the above compositions. In an alternative embodiment, the composition can be diluted with physiological saline.

[0028] These compositions can be used by themselves or in admixture with one or more medicaments, excipients and/or adjuvants, preferably forming a viscous and lubricating substance that remains adherent to the surface epithelium. These compositions are suitable for topical administration to epithelial surfaces such as, but not limited to, the oropharynx and oesophagus.

[0029] A further aspect of the invention concerns the use of hyaluronic acid, or a pharmaceutically acceptable salt thereof, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof, for treating or preventing inflammation in a patient. In one embodiment, the inflammation is of epithelial surfaces such as, but not limited to, the oral mucosa, particularly mucositis and stomatitis.

[0030] Preferably, the compositions of the present invention are administered by topical application.

[0031] The compositions of the invention are preferably in the form of a slightly viscous aqueous liquid (gel) which provides a film-forming and coating effect on the epithelial surfaces such as, but not limited to the oral mucosa.

[0032] As explained above, the present invention relates to a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 and 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment, the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about K85 and K95 and is from about 3 and 10% by weight of the composition. Most preferably, the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about 7 to about 10% by weight of the composition. Preferably, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01 to about 2% by weight. In one embodiment, the viscosity of the composition is from about 90 to about 1000 centipoise. Preferably, the composition is in the form of a gel. Most preferably, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01 to about 2% by weight of the composition, the viscosity of the composition is from about 90 to about 1000 centipoise and the composition is in the form of a gel. Further, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, can be present in weight percentages ranging from about 0.01 to about 3% by weight of the composition.

[0033] In an embodiment of the present invention, the compositions are provided in a concentrated form for later dilution with water. The compositions comprise from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof, and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. These compositions preferably comprise polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof, from about K85 to about K95 and from about 6 to about 12% by weight of the composition, most preferably from about 8 to about 10% by weight of the composition; and comprise hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition. Preferably, hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons in molecular weight and from about 0.04 to about 2% by weight of the composition.

[0034] Examples of pharmaceutically acceptable salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The terim "pharmaceutically acceptable salt" also refers to a salt prepared from a compound having an acidic functional group, such as a carboxylic acid or sulfonic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butylamine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N, N,-dimethyl-N-

(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

[0035] The compositions of the present inventions can comprise a pharmaceutically acceptable excipient, preferably for topical administration, such as one or more of the following:

[0036] viscosity-increasing agent;

[0037] surfactant;

[0038] stabilizing agent/preservative;

[0039] flavor, fragrance, sweetening agent;

[0040] bioadhesive;

[0041] co-solubilizer.

[0042] Examples of said excipients comprise cellulose derivatives, acrylic or methacrylic acids polymers or copolymers, ethylene or propylene glycols, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrins, sodium saccharin, aspartame and other excipients conventionally used in the formulation of collutories or liquid oral forms. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Additional examples of suitable excipients are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

[0043] The compositions of the present invention may further comprise one or more other active ingredients, such as an antibacterial, disinfectant, antifungal, analgesic, other anti-inflammatory, emollients, local anaesthetics and the like. Suitable antimicrobials include, but are not limited to, quaternary ammonium salts such as benzalkonium chloride.

[0044] The precise dose to be employed in the composition will depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. In principle, however, for oral applications, a wash or gargle with 10-50 ml of solution, optionally diluted in water, for a time of about up to two or three minutes at least two but preferably three times or more daily, most preferably before meals, will be sufficient to provide an optimal therapeutic or preventive response. The treatment can be protracted until remission of symptoms, usually for at least 2 days, but preferably 5-10 days. More prolonged treatments are not contraindicated, considering the low, if any, toxicity of the components of the formulations of the invention.

[0045] The present invention also provides a pharmaceutical pack or kit comprising one or more containers, e.g., a flexible packet, vial, ampoule, bottle and the like, filled with one or more of the ingredients of the compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In a preferred embodiment, the compositions of the present invention can be presented as single- or multi-dose forms in a flexible packet. Preferably, the compositions of the present invention are packaged in the concentrated form in flexible packets with a dose of from about 10 to about 30 ml per packet that can be diluted with water to create about 40-60 ml of product for use by the patient.

[0046] The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

EXAMPLE 1

[0047] Qualitative-quantitative composition percent composition:

Ingredient	% By Weight
Sodium hyaluronate	0.1
Glycyrrhetinic acid	0.06
PVP (K60 to K100)	9.0
Maltodextrin	6.00
Propylene glycol	2.94
Potassium sorbate	0.3
Sodium benzoate	0.3
Hydroxyethyl cellulose	1.5
Hydrogenated castor oil PEG-40	0.27
Disodium EDTA	0.1
Benzalkonium chloride	0.5
Perfume (Glycyrrhiza Comp. 2717)	0.16
Sodium saccharin	0.1
Depurated water	78.44

[0048] To prepare this composition, water was placed in a turboemulsifier, then a mixture of potassium sorbate, sodium benzoate and disodium EDTA was added, followed by hyaluronic acid and maltodextrin. The mixture was stirred after each addition until complete dissolution of the components. After that, PVP was slowly added under stirring and vacuum (30 mm Hg) until complete solvation. Then sodium saccharin and hydroxyethylcellulose were subsequently added, the whole was subjected to vacuum and left under stirring until complete salvation. Afterwards, hydrogenated castor oil 40/OE and perfume, benzalkonium chloride, and a mixture of propylene glycol and glycyrrhetinic acid were added in that order, stirring after each addition until complete dissolution of the components. When the additions were completed, the mixture was stirred under vacuum for 30 minutes.

[0049] For a concentrated version of the invention, 10 ml or 15 ml of the above composition were distributed in a packet or mono-dose vial, which can be diluted with 30-50 ml of water before use; for the ready-to-use version, the composition disclosed above was diluted with depurated water to a concentration of 50%, and 200 ml or 300 ml of the resulting composition were distributed in bottles.

EXAMPLE 2

IN VIVO DATA

[0050] Thirty patients, of age range from 30 to 60 years, were evaluated, 10 of them were AIDS patients 30 to 40 years of age who were also receiving anti-retroviral therapy.

All patients in the study were affected with inflammatory pathologies of the oral cavity of various aetiology:

[0051] 12 cases of oro-pharyngeal mucositis;

[0052] 4 cases of aphthous lesions of the oral cavity;

[0053] 4 cases of post-traumatic lesions;

[0054] 3 cases of Lichen Planus of the oral cavity;

[0055] 3 cases of radiotherapy-induced stomatitis;

[0056] 3 cases of oral cavity surgery side effects; and

[0057] 1 case of leukoplakia.

[0058] Patients were treated with the composition described in Example 1 in 15 ml sachets (packets) diluted in water in a 1:4 ratio. The slightly viscous solution was retained in the mouth for 2-3 minutes during which it was gargled and swirled about to obtain homogeneous distribution on the whole surface of the oral mucosa. The solution was then discharged. The patients refrained from eating or drinking for about at least 15 minutes after gargling.

[0059] The formulation was used three times a day 60 minutes before meal times for seven consecutive days.

[0060] At the end of the treatment, the extent of inflammation and lesions, the decrease or disappearance of dysphagia for solid and semi-solid foods, and liquids, and the duration of the activity of the product were evaluated.

[0061] After the first administration, more than 80% of patients perceived within a few hours reduction of pain so as to permit food intake. The effect lasted three or four hours.

[0062] Healing of the lesions of the oral mucosa occurred after 3-4 days of treatment in about 60% of treated cases. The percentage reached 90% at the end of one week of treatment. In the remaining three cases only a pathological condition persisted, but with improved symptoms compared with the beginning of the treatment, providing a remarkable improvement of life quality and restoring a normal, differentiated diet.

EXAMPLE 3

[0063] Two patients with throat pain (sore throat) were unable to obtain relief with analgesics or other topical agents. Patients were treated with the composition described in Example 1 in 15 ml packets, the contents of which were diluted in water in a 1:4 ratio. The solution was retained in the mouth for about one minute during which time it was gargled to obtain good contact with the tissues of the throat. The solution was then discharged. Within ten minutes, the patients experienced dramatic relief of their sore throat symptoms, which relief persisted for several hours.

[0064] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[0065] Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A composition, comprising:

from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 and 2.2 million daltons;

from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and

from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

2. The composition of claim 1, wherein the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about K85 to about K95 and is from about 3 to about 10% by weight of the composition.

3. The composition of claim 2, wherein the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about 7 to about 10% by weight of the composition.

4. The composition of claim 1, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons, and from about 0.01 to about 2% by weight of the composition, and wherein the viscosity of the composition is from about 90 to about 1000 centipoise.

5. The composition of claim 4, in the form of a gel.

6. The composition of claim 3, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01% to about 2% by weight of the composition, and wherein the viscosity of the composition is from about 90 to about 1000 centipoise.

7. The composition of claim 6, in the form of a gel.

8. A composition comprising:

from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, with a molecular weight from about 1.6 to about 2.2 million daltons;

from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof, and

from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

9. The composition of claim 8, wherein the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about K85 to about K95, and is from about 6 to about 12% by weight of the composition.

10. The composition of claim 9, wherein the polyvinylpyrrolidone, or the pharmaceutically acceptable salt thereof, is from about 8 to about 10% by weight of the composition.

11. The composition of claim 8, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition.

12. The composition of claim 11, in the form of a gel.

13. The composition of claim 10, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from

about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition.

14. The composition of claim 13, in the form of a gel.

15. A flexible packet comprising the composition of claim 8.

16. The packet of claim 15, being a sealed pouch comprising from about 10 to about 30 milliliters of the composition.

17. A composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone or a pharmaceutically acceptable salt thereof.

18. The composition of claim 17, further comprising a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavour, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer.

19. The composition of claim 18, further comprising a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame.

20. The composition of claim 17, further comprising an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

21. A method for treating or preventing inflammation in a patient comprising:

administering to a patient in need thereof an effective amount of a composition comprising:

(i) from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons;

(ii) from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone, or a pharmaceutically acceptable salt thereof; and

(iii) from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

22. The method of claim 21, wherein the composition is administered at least twice daily for at least two consecutive days.

23. The method of claim 21, wherein the composition is administered at least three times daily for at least four consecutive days.

24. A method for treating or preventing inflammation in a patient, comprising administering to a patient in need thereof an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone or a pharmaceutically acceptable salt thereof.

25. The method of claim 21, wherein the administration is by topical application.

26. The method of claim 24, wherein the administration is by topical application.

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US 20020183278A1

(19) United States

(12) Patent Application Publication (10) Pub. No.: US 2002/0183278 A1

Mastrodonato et al. (43) Pub. Date: Dec. 5, 2002

(54) COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF INFLAMMATION

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(21) Appl. No.: 10/080,736

(22) Filed: Feb. 22, 2002

Related U.S. Application Data

(63) Continuation-in-part of application No. 10/080,624, filed on Feb. 21, 2002.

(30) Foreign Application Priority Data

Jul. 28, 2000 (IT) ..... MI 2000 A 001732

Publication Classification

(51) Int. Cl.[7] A61K 31/728; A61K 31/79

(52) U.S. Cl. 514/54; 424/78.32

(57) ABSTRACT

The present invention relates to compounds containing as active ingredients hyaluronic acid and polyvinylpyrrolidone, for the treatment of inflammatory, ulcerative and painful conditions of moist epithelial surfaces such as mucositis, stomatitis, vestibulitis, aphthous ulcerations, and Behcet's syndrome.

COMPOSITIONS AND METHODS FOR THE TREATMENT OR PREVENTION OF INFLAMMATION

[0001] The present application is a continuation-in-part of Pennie & Edmonds LLP Docket No. 10142-007, filed on Feb. 21, 2002, which claims priority benefits of International Patent Application No. PCT/EP01/08303 filed Jul. 18, 2001, (published as WO 02/09637 in English on Feb. 7, 2002), which in turn claims priority benefits of Italian Patent Application No. MI 2000 A 001732, filed Jul. 28, 2000, the disclosures of each of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] This invention relates to certain compositions useful for the management of painful ulcerative and inflammatory conditions of moist surfaces including the mouth, oropharynx, oesophagus, vagina and rectum (including, but not limited to, mucositis, stomatitis, aphthous ulcerations, and Behcet's syndrome).

BACKGROUND OF THE INVENTION

[0003] Aggressive cancer treatment may have toxic effects on normal cells as well as cancer cells. The gastrointestinal tract, including the mouth, is especially affected because these cells are replaced by the body continuously.

[0004] Mucositis, an inflammation of the mucous membranes in the mouth, is one of the most common oral problems occurring after chemotherapy and radiation therapy. Mucositis can contribute to oral infections, inability to taste normally and pain arising from the resulting open sores that can develop. Mucositis can become so painful that the patient will not eat or drink, contributing to dehydration and malnutrition.

[0005] Radiation therapy to the head and neck for cancers in those areas commonly injure saliva glands and the inside of the mouth which can cause dry mouth, leading to dental disease.

[0006] The mucositis problem is not restricted to cancer patients, as mucositis frequently also occurs in HIV patients, particularly when associated with Kaposi's sarcoma, in patients affected with non-Hodgkin's lymphoma, in debilitated elderly patients and in patients receiving BRM treatments like interleukin-2, TNF, interferons, lymphokine-activated lymphocytes and the like.

[0007] Such oral problems may make it difficult for the cancer or AIDS patient to receive a complete dose of chemotherapy or radiation therapy. Sometimes treatment must be stopped completely. Such problems are not infrequent: about half of the patients have severe oral lesions that require medical intervention, mostly involving the changes in cancer medication or treatment mentioned above.

[0008] Current therapies for mucositis are limited. Cleaning the mouth is recommended to retard the progression of the condition.

[0009] Oral cleaning care includes gently cleaning the mouth, moisturizing the lips and mouth, and relieving pain and swelling. A soft toothbrush or toothette cleans teeth well and gently. Cleansing agents can include "salt and soda" (½ tsp. salt and 2 Tbs. of sodium bicarbonate in 32 oz. of warm water), normal saline, sterile water, or sodium bicarbonate (1 tsp. in 8 oz of water). Hydrogen peroxide diluted in equal amounts of water or weak salt water can be used when crusting is present. (This should be used for 1 or 2 days only because it will keep mucositis from healing.) Gentle wiping with a wet gauze dipped in salt water helps remove particles. Toothettes may be too rough for some areas. Particles should be removed before ointments or other medications are put onto the gums or tissues. Rinsing often cleans and moistens the tissues, prevents crusting, and soothes sore gums and tissues. Frequent rinsing prevents particles and bacteria from collecting in the mouth. A salt and baking soda solution neutralizes acids and dissolves thick saliva.

[0010] Capsaicin, the active ingredient in hot peppers, reportedly has used to increase a person's ability to tolerate pain. When capsaicin is put on inflamed tissues in the mouth, mucositis pain may decrease as the burning feeling from the capsaicin decreases. Capsaicin is only being used experimentally; however, all side effects are not known.

[0011] Mostly, physicians have resorted ice chips or to rather makeshift mixtures of benzocaine with kaopectate and the like. These approaches provide rather limited, temporary relief.

[0012] Carrington Laboratories of Irving, Tex. has sold a mucositis product called "Radiacare" for a number of years. However, this product has made limited inroads into the marketplace, and thus has provided few patients relief from the symptoms of mucositis.

[0013] Many women get oral aphthous ulceration at specific times of the menstrual cycle and simultaneously get the same kind of ulcers in the genital tract, in particular the vulva and vagina. This is sometimes very severe and can cause retention of urine and require strong painkillers and sedatives. The most severe form is called Behcet's syndrome.

[0014] The terms mucositis and stomatitis are often used interchangeably but may include some general distinctions. Mucositis describes a toxic inflammatory reaction affecting the gastrointestinal tract, which may result from exposure to chemotherapeutic agents or ionising radiation. Mucositis typically manifests as an erythematous, burn-like lesion or as random, focal-to-diffuse, ulcerative lesions. Stomatitis refers to an inflammatory reaction affecting the oral mucosa, with or without ulceration, that may be caused or intensified by pharmacological, particularly chemotherapeutic treatments, or by radiotherapy. Stomatitis can range from mild to severe; the patient with severe stomatitis is unable to take anything by mouth.

[0015] Thus, there is a clear need for compositions and methods useful for treating or preventing inflammation, including but not limited to, mucositis, stomatitis, aphthous ulcerations, Behcet's syndrome, etc.

[0016] Citation of a reference in this or any section of the specification shall not be construed as an admission that such reference is prior art to the present invention.

SUMMARY OF THE INVENTION

[0017] The present invention is directed to a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt

thereof, having a molecular weight from about 1.6 and 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment the polyvinylpyrrolidone is from about K85 to about K95 and is from about 3 to about 10% by weight of the composition. In another embodiment, the polyvinylpyrrolidone is from about 7 to about 10% by weight of the composition. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons, and from about 0.01 to about 2% by weight of the composition, and wherein the viscosity of the composition is from about 90 to about 1000 centipoise. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01% to about 2% by weight of the composition. In an embodiment, the viscosity of the composition is from about 90 to about 1000 centipoise. In a preferred embodiment, the composition is in the form of a gel.

[0018] The present invention is also directed to a composition comprising from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, with a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment, the polyvinylpyrrolidone, is from about K85 to about K95, and is from about 6 to about 12% by weight of the composition. In another embodiment, the polyvinylpyrrolidone is from about 8 to about 10% by weight of the composition. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition. In yet another embodiment, the hyaluronic acid, or the pharmaceutically acceptable salt thereof is from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition. In a preferred embodiment, the composition is in the form of a gel.

[0019] The present invention is also directed to a flexible packet comprising a composition comprising from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, with a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In a preferred embodiment, the packet is a sealed pouch comprising from about 10 to about 30 milliliters of the composition. The present invention is also directed to a flexible packet comprising a composition comprising hyaluronic acid, or a pharmaceutically acceptable salt thereof, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone.

[0020] The present invention is also directed to a composition comprising hyaluronic acid, or a pharmaceutically acceptable salt thereof, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone. In an embodiment, the composition further comprises a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavor, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer. The composition may also further comprise a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame. In yet another embodiment, the composition further comprises an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

[0021] The present invention is also directed to a method for treating or preventing inflammation in a patient comprising administering to a patient in need thereof an effective amount of a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment, the composition is administered at least twice daily for at least two consecutive days. In yet another embodiment, the composition is administered at least three times daily for at least four consecutive days. In yet another embodiment, the composition is administered at least three times daily for at least seven consecutive days.

[0022] The present invention is also directed to a method for treating or preventing inflammation in a patient, comprising administering to a patient in need thereof an effective amount of a composition comprising hyaluronic acid, or a pharmaceutically acceptable salt thereof, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone. In an embodiment, the composition is administered at least twice daily for at least two consecutive days. In yet another embodiment, the composition is administered at least three times daily for at least four consecutive days. In yet another embodiment, the composition is administered at least three times daily for at least seven consecutive days. In addition to its ordinary meaning, the term treatment encompasses inhibition of progression of symptoms or amelioration of symptoms of inflammation and mucositis.

[0023] The present invention is also directed to a method for treating or preventing inflammation in the oral cavity of a patient comprising having a patient in need thereof gargle an effective amount of a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. The present invention is also directed to a method for treating or preventing inflammation in the oral cavity of a patient comprising having a patient in need thereof gargle an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone.

[0024] The present invention is directed to a method for treating or preventing mucositis in a patient comprising administering to a patient in need thereof an effective amount of a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. The present invention is also directed to a method for treating or preventing mucositis in a patient comprising administering to a patient in need thereof an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone.

[0025] The present invention is directed to a method for treating pain resulting from oral surgery in a patient in need thereof comprising having a patient in need thereof gargle an effective amount of a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. The present invention is also directed to a method for treating pain resulting from oral surgery in a patient in need thereof comprising having a patient in need thereof gargle an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone.

[0026] The present invention can be more fully explained by reference to the following detailed description and illustrative examples.

DETAILED DESCRIPTION OF THE INVENTION

[0027] Surprisingly, the topical administration of a formulation comprising an effective amount of hyaluronic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone provides an effective therapeutical or preventive treatment for mucositis and stomatitis of various origin and severity and, more generally, of the lesions of the oro-pharynx cavity and oesophagus, particularly those caused by dental devices and by radio- or chemotherapy and by surgery.

[0028] Without being bound by a particular mode of action, the favorable therapeutic results obtained by the use of the compositions of the present invention are believed to be due to both the interactions between hyaluronic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone, and the capability of the formulation of adhering to the oral mucosa providing a protective coating for the exposed nerve endings, and thus, reduction of pain and promoting cicatrisation and healing of the lesions. Furthermore, it is believed that the moisturizing effect of the compositions has beneficial effect as it protects mucous membranes from further irritating lesions.

[0029] In one embodiment, the present invention involves a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise.

[0030] In an alternative embodiment, the present invention involves a composition comprising from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. The compositions of the present invention can be diluted with water, and accordingly, is useful for obtaining the above compositions. In an alternative embodiment, the composition can be diluted with physiological saline.

[0031] These compositions can be used by themselves or in admixture with one or more medicaments, excipients and/or adjuvants, preferably forming a viscous and lubricating substance that remains adherent to the surface epithelium. These compositions are suitable for topical administration to epithelial surfaces such as, but not limited to, the oropharynx and oesophagus.

[0032] A further aspect of the invention concerns the use of hyaluronic acid, or a pharmaceutically acceptable salt thereof, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone for treating or preventing inflammation in a patient. In one embodiment, the inflammation is of epithelial surfaces such as, but not limited to, the oral mucosa, particularly mucositis and stomatitis.

[0033] Preferably, the compositions of the present invention are administered by topical application. In a particular embodiment in which the composition is administered to the oral cavity, the patient, after gargling with the composition, and if desired, may refrain from eating or drinking for a certain time, ranging from minutes up to hours after gargling. Alternatively, the patient, if desired, may eat or drink immediately after gargling.

[0034] The compositions of the invention are preferably in the form of a slightly viscous aqueous liquid (gel) which provides a film-forming and coating effect on the epithelial surfaces such as, but not limited to the oral mucosa.

[0035] As explained above, the present invention relates to a composition comprising from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 and 2.2 million daltons; from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. In an embodiment, the polyvinylpyrrolidone is from about K85 and K95 and is from about 3 and 10% by weight of the composition. Most preferably, the polyvinylpyrrolidone is from about 7 to about 10% by weight of

the composition. Preferably, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01 to about 2% by weight. In one embodiment, the viscosity of the composition is from about 90 to about 1000 centipoise. Preferably, the composition is in the form of a gel. Most preferably, the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01 to about 2% by weight of the composition, the viscosity of the composition is from about 90 to about 1000 centipoise and the composition is in the form of a gel. Further, glycyrrhetinic acid, or a pharmaceutically acceptable salt thereof, can be present in weight percentages ranging from about 0.01 to about 3% by weight of the composition.

[0036] The viscosity of the compositions can be measured using routine methods. In particular, viscosity can be measured using a Brookfield Model DV1+ viscometer (Middleboro, Mass.) at room temperature, preferably at about 22°-25° C., or using a Haake Model VT02 viscometer (Karlsruhe, Germany) at room temperature, preferably at about 22°-25° C.

[0037] In a particular embodiment of the present invention, the compositions are provided in a concentrated form for later dilution with water. The compositions comprise from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons; from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and from about 86 to about 98% water. In one embodiment, the viscosity of the composition is from about 50 to about 500 centipoise. These compositions preferably comprise polyvinylpyrrolidone from about K85 to about K95 and from about 6 to about 12% by weight of the composition, most preferably from about 8 to about 10% by weight of the composition; and comprise hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition. Preferably, hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons in molecular weight and from about 0.04 to about 2% by weight of the composition.

[0038] Examples of pharmaceutically acceptable salts include, but are not limited to, sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate, and pamoate (i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. The term "pharmaceutically acceptable salt" also refers to a salt prepared from a compound having an acidic functional group, such as a carboxylic acid or sulfonic acid functional group, and a pharmaceutically acceptable inorganic or organic base. Suitable bases include, but are not limited to, hydroxides of alkali metals such as sodium, potassium, and lithium; hydroxides of alkaline earth metal such as calcium and magnesium; hydroxides of other metals, such as aluminum and zinc; ammonia, and organic amines, such as unsubstituted or hydroxy-substituted mono-, di-, or trialkylamines; dicyclohexylamine; tributyl amine; pyridine; N-methyl,N-ethylamine; diethylamine; triethylamine; mono-, bis-, or tris-(2-hydroxy-lower alkyl amines), such as mono-, bis-, or tris-(2-hydroxyethyl)amine, 2-hydroxy-tert-butyl amine, or tris-(hydroxymethyl)methylamine, N, N,-di-lower alkyl-N-(hydroxy lower alkyl)-amines, such as N, N,-dimethyl-N-(2-hydroxyethyl)amine, or tri-(2-hydroxyethyl)amine; N-methyl-D-glucamine; and amino acids such as arginine, lysine, and the like.

[0039] The compositions of the present inventions can comprise a pharmaceutically acceptable excipient, preferably for topical administration, such as one or more of the following:

[0040] viscosity-increasing agent;

[0041] surfactant;

[0042] stabilizing agent/preservative;

[0043] flavor, fragrance, sweetening agent;

[0044] bioadhesive;

[0045] co-solubilizer.

[0046] Examples of said excipients comprise cellulose derivatives, acrylic or methacrylic acids polymers or copolymers, ethylene or propylene glycols, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrins, sodium saccharin, aspartame and other excipients conventionally used in the formulation of collutories or liquid oral forms. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Additional examples of suitable excipients are described in "Remington's Pharmaceutical Sciences" by E. W. Martin.

[0047] The compositions of the present invention may further comprise one or more other active ingredients, such as an antibacterial, disinfectant, antifungal, analgesic, other anti-inflammatory, emollients, local anaesthetics and the like. Suitable antimicrobials include, but are not limited to, quaternary ammonium salts such as benzalkonium chloride.

[0048] The precise dose to be employed in the composition will depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. In principle, however, for oral applications, a wash or gargle with 10-50 ml of solution, optionally diluted in water, for a time of about up to two or three minutes at least two but preferably three times or more daily, most preferably before meals, will be sufficient to provide an optimal therapeutic or preventive response. The treatment can be protracted until remission of symptoms, usually for at least 2 days, but preferably 5-10 days. More prolonged treatments are not contraindicated, considering the low, if any, toxicity of the components of the formulations of the invention.

[0049] The present invention also provides a pharmaceutical pack or kit comprising one or more containers, e.g. a flexible packet, vial, ampoule, bottle and the like, filled with one or more of the ingredients of the compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or

biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In a preferred embodiment, the compositions of the present invention can be presented as single- or multi-dose forms in a flexible packet. Preferably, the compositions of the present invention are packaged in the concentrated form in flexible packets with a dose of from about 10 to about 30 ml per packet that can be diluted with water to create about 40-60 ml of product for use by the patient.

[0050] The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

EXAMPLE 1

[0051] Qualitative-quantitative composition percent composition:

Ingredient	% By Weight
Sodium hyaluronate	0.1
Glycyrrhetinic acid	0.06
PVP (K 60 to K 100)	9.0
Maltodextrin	6.00
Propylene glycol	2.94
Potassium sorbate	0.3
Sodium benzoate	0.3
Hydroxyethyl cellulose	1.5
Hydrogenated castor oil PEG-40	0.27
Disodium EDTA	0.1
Benzalkonium chloride	0.5
Perfume (Glycyrrhiza Comp. 2717)	0.16
Sodium saccharin	0.1
Depurated water	78.44

[0052] To prepare this composition, water was placed in a turboemulsifier, then a mixture of potassium sorbate, sodium benzoate and disodium EDTA was added, followed by hyaluronic acid and maltodextrin. The mixture was stirred after each addition until complete dissolution of the components. After that, PVP was slowly added under stirring and vacuum (30 mm Hg) until complete solvation. Then sodium saccharin and hydroxyethylcellulose were subsequently added, the whole was subjected to vacuum and left under stirring until complete solvation. Afterwards, hydrogenated castor oil 40/OE and perfume, benzalkonium chloride, and a mixture of propylene glycol and glycyrrhetinic acid were added in that order, stirring after each addition until complete dissolution of the components. When the additions were completed, the mixture was stirred under vacuum for 30 minutes.

[0053] For a concentrated version of the invention, 10 ml or 15 ml of the above composition were distributed in a packet or mono-dose vial, which can be diluted with 30-50 ml of water before use; for the ready-to-use version, the composition disclosed above was diluted with depurated water to a concentration of 50%, and 200 ml or 300 ml of the resulting composition were distributed in bottles.

EXAMPLE 2

[0054] In vivo Data

[0055] Thirty patients, of age range from 30 to 60 years, were evaluated, 10 of them were AIDS patients 30 to 40 years of age who were also receiving anti-retroviral therapy. All patients in the study were affected with inflammatory pathologies of the oral cavity of various aetiology:

[0056] 12 cases of oro-pharyngeal mucositis;

[0057] 4 cases of aphthous lesions of the oral cavity;

[0058] 4 cases of post-traumatic lesions;

[0059] 3 cases of Lichen Planus of the oral cavity;

[0060] 3 cases of radiotherapy-induced stomatitis;

[0061] 3 cases of oral cavity surgery side effects; and

[0062] 1 case of leukoplakia.

[0063] Patients were treated with the composition described in Example 1 in 15 ml sachets (packets) diluted in water in a 1:4 ratio. The slightly viscous solution was retained in the mouth for 2-3 minutes during which it was gargled and swirled about to obtain homogeneous distribution on the whole surface of the oral mucosa. The solution was then discharged. The patients refrained from eating or drinking for various times after gargling ranging from immediately after gargling to more than 1 hour after gargling.

[0064] The formulation was used three times a day 60 minutes before meal times for seven consecutive days.

[0065] At the end of the treatment, the extent of inflammation and lesions, the decrease or disappearance of dysphagia for solid and semi-solid foods, and liquids, and the duration of the activity of the product were evaluated.

[0066] After the first administration, more than 80% of patients perceived within a few hours reduction of pain so as to permit food intake. The effect lasted three or four hours.

[0067] Healing of the lesions of the oral mucosa occurred after 3-4 days of treatment in about 60% of treated cases. The percentage reached 90% at the end of one week of treatment. In the remaining three cases only a pathological condition persisted, but with improved symptoms compared with the beginning of the treatment, providing a remarkable improvement of life quality and restoring a normal, differentiated diet.

EXAMPLE 3

[0068] Two patients with throat pain (sore throat) were unable to obtain relief with analgesics or other topical agents. Patients were treated with the composition described in Example 1 in 15 ml packets, the contents of which were diluted in water in a 1:4 ratio. The solution was retained in the mouth for about one minute during which time it was gargled to obtain good contact with the tissues of the throat. The solution was then discharged. Within ten minutes, the patients experienced dramatic relief of their sore throat symptoms, which relief persisted for several hours.

[0069] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

[0070] Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

What is claimed is:

1. A composition, comprising:

from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 and 2.2 million daltons;

from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and

from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

2. The composition of claim 1, wherein the polyvinylpyrrolidone is from about K85 to about K95 and is from about 3 to about 10% by weight of the composition.

3. The composition of claim 2, wherein the polyvinylpyrrolidone is from about 7 to about 10% by weight of the composition.

4. The composition of claim 1, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons, and from about 0.01 to about 2% by weight of the composition, and wherein the viscosity of the composition is from about 90 to about 1000 centipoise.

5. The composition of claim 4, in the form of a gel.

6. The composition of claim 3, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.01% to about 2% by weight of the composition, and wherein the viscosity of the composition is from about 90 to about 1000 centipoise.

7. The composition of claim 6, in the form of a gel.

8. The composition of claim 1, further comprising a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavour, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer.

9. The composition of claim 8, further comprising a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame.

10. The composition of claim 1, further comprising an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

11. The composition of claim 1, further comprising glycyrrhetinic acid or a pharmaceutically acceptable salt thereof.

12. A composition comprising:

from about 0.04 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, with a molecular weight from about 1.6 to about 2.2 million daltons;

from about 0.08 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and

from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

13. The composition of claim 12, wherein the polyvinylpyrrolidone is from about K85 to about K95, and is from about 6 to about 12% by weight of the composition.

14. The composition of claim 13, wherein the polyvinylpyrrolidone is from about 8 to about 10% by weight of the composition.

15. The composition of claim 12, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition.

16. The composition of claim 15, in the form of a gel.

17. The composition of claim 14, wherein the hyaluronic acid, or the pharmaceutically acceptable salt thereof, is from about 1.8 to about 2.0 million daltons and from about 0.04 to about 2% by weight of the composition.

18. The composition of claim 17, in the form of a gel.

19. The composition of claim 12, further comprising a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavour, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer.

20. The composition of claim 19, further comprising a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame.

21. The composition of claim 12, further comprising an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

22. The composition of claim 12, further comprising glycyrrhetinic acid or a pharmaceutically acceptable salt thereof.

23. A flexible packet comprising the composition of claim 12.

24. The packet of claim 23, being a sealed pouch comprising from about 10 to about 30 milliliters of the composition.

25. A composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone.

26. A flexible packet comprising the composition of claim 25.

27. The composition of claim 25, further comprising a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavour, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer.

28. The composition of claim 27, further comprising a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame.

29. The composition of claim 25, further comprising an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

30. A method for treating or preventing inflammation in a patient comprising:

administering to a patient in need thereof an effective amount of a composition comprising:

(i) from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable

salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons;

(ii) from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and

(iii) from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

31. The method of claim 30, wherein the composition is administered at least twice daily for at least two consecutive days.

32. The method of claim 30, wherein the composition is administered at least three times daily for at least four consecutive days.

33. The method of claim 30, wherein the composition is administered at least three times daily for at least seven consecutive days.

34. The method of claim 30, wherein the composition further comprises a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavour, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer.

35. The method of claim 34, wherein the composition further comprises a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame.

36. The method of claim 30, wherein the composition further comprises an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

37. The method of claim 30, wherein the administration is by topical application.

38. The method of claim 30, wherein the composition further comprises glycyrrhetinic acid or a pharmaceutically acceptable salt thereof.

39. A method for treating or preventing inflammation in a patient, comprising administering to a patient in need thereof an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone.

40. The method of claim 39, wherein the administration is by topical application.

41. The method of claim 39, wherein the composition is administered at least twice daily for at least two consecutive days.

42. The method of claim 39, wherein the composition is administered at least three times daily for at least four consecutive days.

43. The method of claim 39, wherein the composition is administered at least three times daily for at least seven consecutive days.

44. The method of claim 39, wherein the composition further comprises a viscosity-increasing agent, surfactant, stabilizing agent/preservative, flavour, fragrance, sweetening agent, bioadhesive agent, or a co-solubilizer.

45. The method of claim 44, wherein the composition further comprises a cellulose derivative, acrylic or methacrylic acid polymer or copolymer, ethylene or propylene glycol, polyethoxylated hydrogenated castor oil, EDTA, sodium benzoate, sodium or potassium sorbate, dextrin, sodium saccharin, or aspartame.

46. The method of claim 39, wherein the composition further comprises an antibacterial agent, disinfectant agent, antifungal agent, analgesic, anti-inflammatory, emollient, or a local anesthetic.

47. A method for treating or preventing inflammation in the oral cavity of a patient comprising:

having a patient in need thereof gargle an effective amount of a composition comprising:

(i) from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons;

(ii) from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and

(iii) from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

48. A method for treating or preventing inflammation in the oral cavity of a patient comprising:

having a patient in need thereof gargle an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof, and polyvinylpyrrolidone.

49. The method of claim 47 or 48, wherein the patient gargles the composition at least twice daily for at least two consecutive days.

50. The method of claim 47 or 48, wherein the patient gargles the composition at least three times daily for at least four consecutive days.

51. The method of claim 47 or 48, wherein the patient gargles the composition at least three times daily for at least seven consecutive days.

52. The method of claim 47, wherein the composition further comprises glycyrrhetinic acid or a pharmaceutically acceptable salt thereof.

53. The method of claim 47 or 48, wherein the patient avoids eating or drinking for at least one hour after gargling.

54. A method for treating or preventing mucositis in a patient comprising:

administering to a patient in need thereof an effective amount of a composition comprising:

(i) from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons;

(ii) from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and

(iii) from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

55. A method for treating or preventing mucositis in a patient comprising:

administering to a patient in need thereof an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone.

56. The method of claim 54 or 55, wherein the composition is administered at least twice daily for at least two consecutive days.

57. The method of claim 54 or 55, wherein the composition is administered at least three times daily for at least four consecutive days.

58. The method of claim 54 or 55, wherein the composition is administered at least three times daily for at least seven consecutive days.

59. The method of claim 54, wherein the composition further comprises glycyrrhetinic acid or a pharmaceutically acceptable salt thereof.

60. A method for treating pain resulting from oral surgery in a patient in need thereof comprising:

having a patient in need thereof gargle an effective amount of a composition comprising:

(i) from about 0.01 to about 5 percent by weight of hyaluronic acid, or a pharmaceutically acceptable salt thereof, having a molecular weight from about 1.6 to about 2.2 million daltons;

(ii) from about 0.04 to about 15% by weight of a K60 to K100 polyvinylpyrrolidone; and

(iii) from about 86 to about 98% water,

wherein the viscosity of the composition is from about 50 to about 500 centipoise.

61. A method for treating pain resulting from oral surgery in a patient in need thereof comprising:

having a patient in need thereof gargle an effective amount of a composition comprising hyaluronic acid or a pharmaceutically acceptable salt thereof; glycyrrhetinic acid or a pharmaceutically acceptable salt thereof; and polyvinylpyrrolidone.

62. The method of claim 60 or 61, wherein the patient gargles the composition at least twice daily for at least two consecutive days.

63. The method of claim 60 or 61, wherein the patient gargles the composition at least three times daily for at least four consecutive days.

64. The method of claim 60 or 61, wherein the patient gargles the composition at least three times daily for at least seven consecutive days.

65. The method of claim 60, wherein the composition further comprises glycyrrhetinic acid or a pharmaceutically acceptable salt thereof.

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